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# A SCIENTIFIC CORNER

WHERE OPTICAL PROBLEMS ARE DISCUSSED AND
THE SOLUTIONS, AS SOLVED BY EXPERIENCE, INDICATED!

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## THICKNESS DIFFERENCE OF PRISMS

There are three methods of determining the prismatic power of a lens; neutralizing with prisms of known power, measuring the displacement power by means of a calibrated scale and calipering the difference in the edge thickness.

The calipering method is simple, requires no elaborate equipment and is quite accurate especially when applied to plano prisms.

A prism is a wedge shaped piece of glass, thicker at the base than at the apex by an amount that is determined by the following formula:

$$T=0.0191 \times P \times D$$

In this formula "T" is the difference in thickness between the base and the apex. "P" is the prism and "D" is the diameter of the lens. The table below was computed from this formula and shows the thickness difference between the base and the apex of knife edge prisms. The table is figured for optical crown glass of index 1.523. For flint glass of index 1.690 multiply the figures given in the table by 0.758.

| Prism | DIAMETER OF LENS | | | | | |
|---|---|---|---|---|---|---|
| | 38 | 40 | 42 | 44 | 46 | 48 |
| 0.5 | 0.36 | 0.38 | 0.40 | 0.42 | 0.44 | 0.46 |
| 1.0 | 0.72 | 0.76 | 0.80 | 0.84 | 0.88 | 0.92 |
| 1.5 | 1.09 | 1.15 | 1.20 | 1.25 | 1.32 | 1.38 |
| 2.0 | 1.45 | 1.53 | 1.61 | 1.68 | 1.76 | 1.84 |
| 2.5 | 1.82 | 1.91 | 2.01 | 2.10 | 2.20 | 2.30 |
| 3.0 | 2.18 | 2.29 | 2.41 | 2.50 | 2.64 | 2.76 |
| 3.5 | 2.54 | 2.67 | 2.81 | 2.92 | 3.08 | 3.22 |
| 4.0 | 2.90 | 3.05 | 3.20 | 3.36 | 3.52 | 3.68 |
| 4.5 | 3.26 | 3.43 | 3.60 | 3.78 | 3.96 | 4.14 |
| 5.0 | 3.62 | 3.81 | 4.00 | 4.20 | 4.40 | 4.60 |
| 6.0 | 4.34 | 4.56 | 4.79 | 5.00 | 5.28 | 5.42 |
| 7.0 | 5.05 | 5.32 | 5.58 | 5.84 | 6.16 | 6.44 |
| 8.0 | 5.76 | 6.10 | 6.37 | 6.72 | 7.04 | 7.36 |
| 9.0 | 6.46 | 6.80 | 7.14 | 7.56 | 7.92 | 8.28 |
| 10.0 | 7.17 | 7.54 | 7.92 | 8.40 | 8.78 | 9.17 |

"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

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THE A. M. A. ARCHIVES OF OPHTHALMOLOGY is published by the American Medical Association to continue the *Archives of Ophthalmology*, founded by Herman Knapp in 1869, and to provide American ophthalmologists with a publication devoted not only to original contributions in the field of ophthalmology but to a survey of the ophthalmologic literature and a review of the transactions of ophthalmologic societies.

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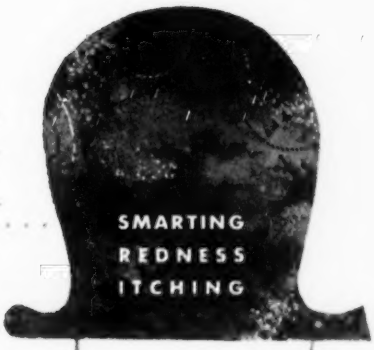

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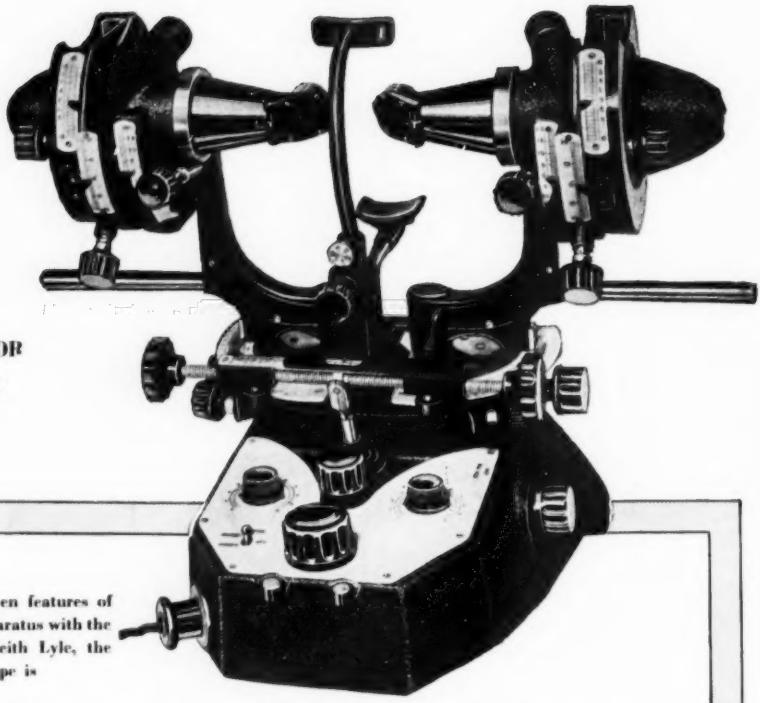

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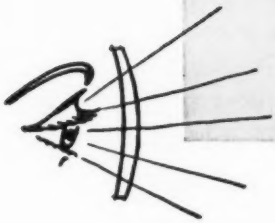

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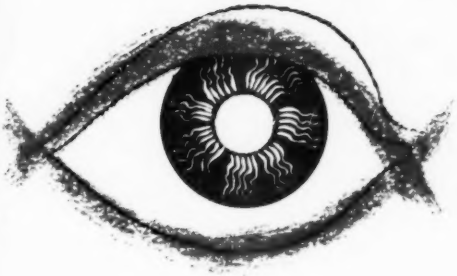

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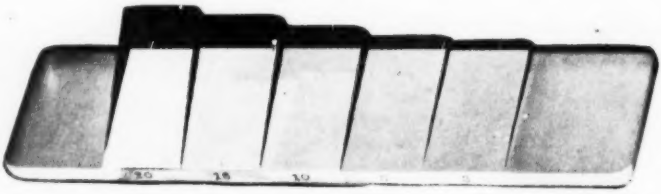

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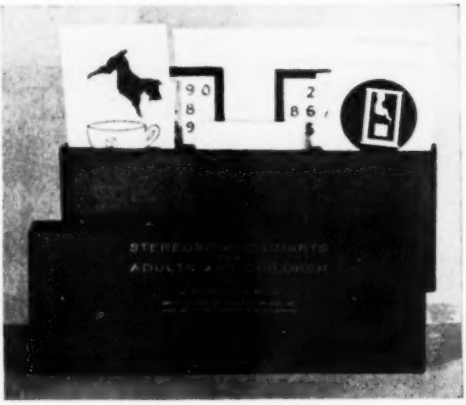

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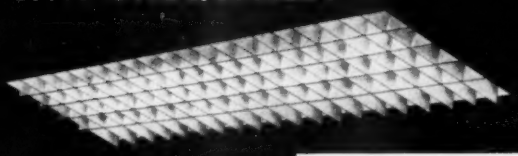

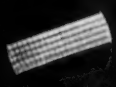

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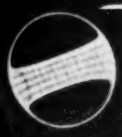

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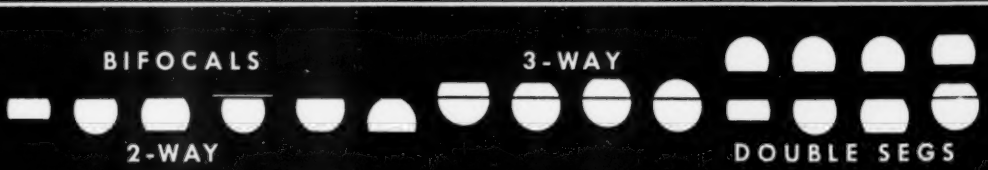

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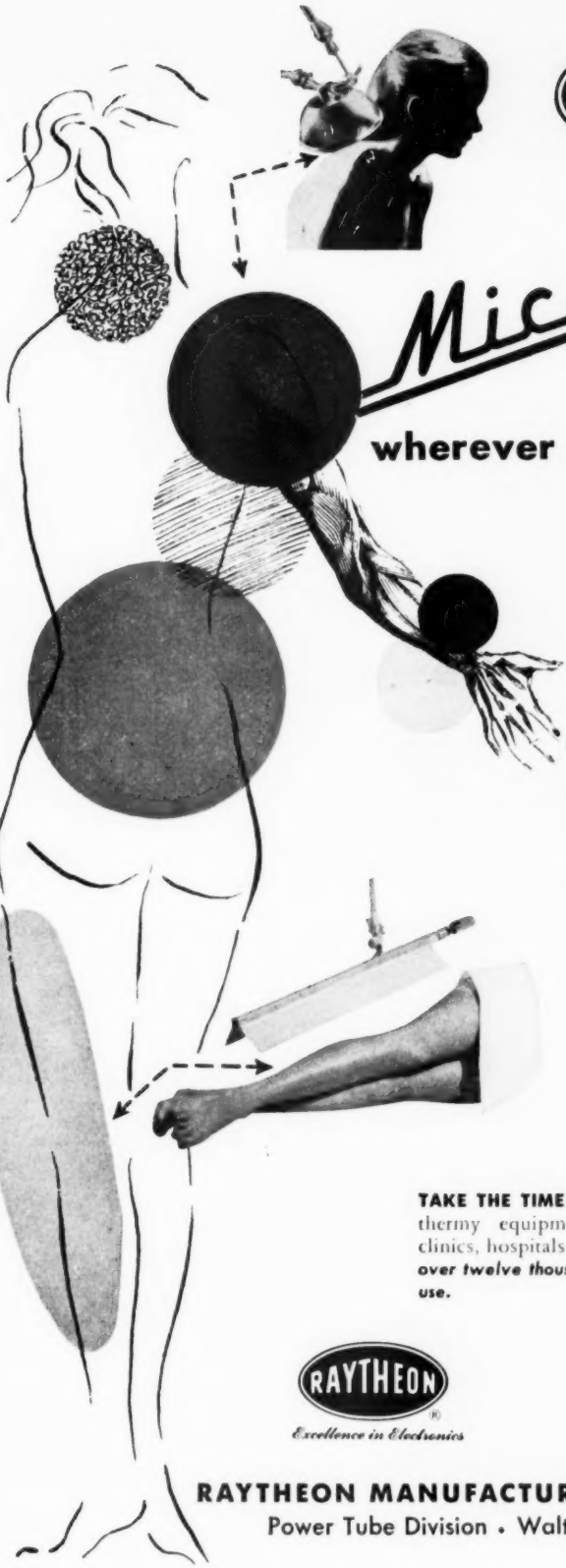

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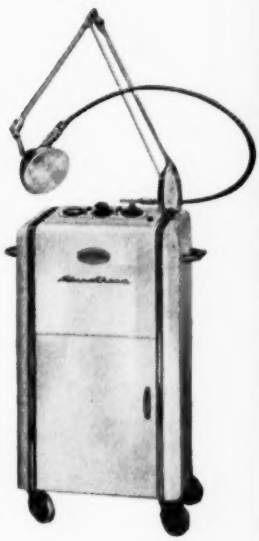

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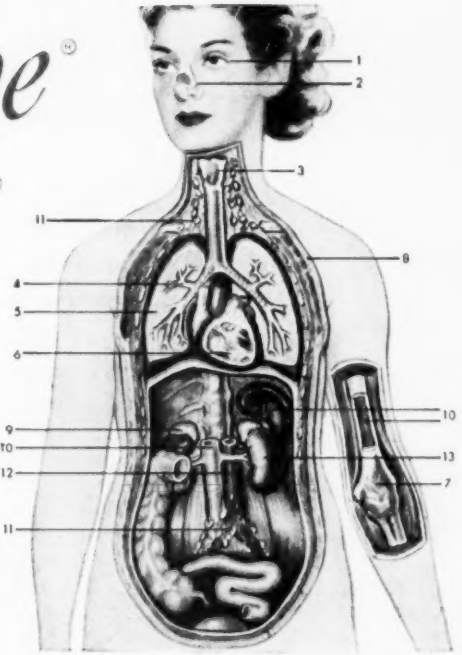


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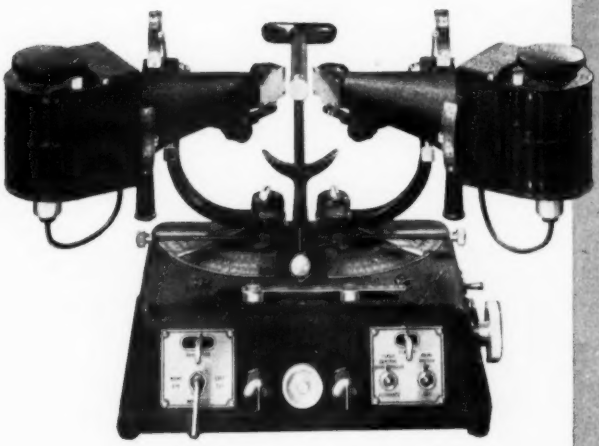

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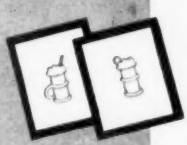

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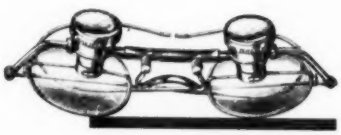

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# ELECTRORETINOGRAPHIC STUDIES IN CASES OF PIGMENTARY DEGENERATION

LIEUTENANT JERRY JACOBSON
MEDICAL CORPS, UNITED STATES AIR FORCE
AND
J. MILES O'BRIEN, M.D.
BRIDGEPORT, CONN.

THE ELECTRICAL response of the vertebrate retina to light has been the subject of physiologic research for some time past. As far back as 1865 Holmgren,[1] in Sweden, was aware of these changes. Later, Dewar and McKendrick,[2] working independently in Scotland, also noted this effect. The work was carried further by many outstanding investigators, but all were hampered by the lack of instruments adequate with regard to sensitivity and amplification. With the advent of the modern radio tube, rapid advances have been made in these studies and have evolved into what is presently known as electroretinography. For the outstanding contribution in this field, the reader is referred to the monograph by Granit,[3] which covers all phases of the work.

Recently, we completed a survey [4] of clinical electroretinography in an effort to determine its use in general clinical practice. Since the method proved both feasible and accurate, it was thought desirable to apply it in the study of some pathologic entity not well understood. From the standpoint of visual destructiveness and absence of effective therapy, pigmentary degeneration of the retina seemed a fitting subject for the survey. The same apparatus was used in this study as in the series we have previously reported.[4]

## THEORETICAL CONSIDERATIONS

Functionally, the retina has two main divisions (Fig. 1): (1) the visual chain, consisting of the receptor (rod or cone), the bipolar cell, and, finally, the ganglion cell, and (2) the synaptic layer, composed of the amacrine cells and the horizontal cells.

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Read before the Section on Ophthalmology at the One Hundred First Annual Session of the American Medical Association, Chicago, June 10, 1952.

1. Holmgren, F.: Metod att objectivera effecten av ljusintryck på retina, Upsala läkaref. förh. **1**:177, 1865; Om retinaströmmen, ibid. **6**:419, 1870-1871.

2. Dewar, J., and McKendrick, J.: On the Physiological Action of Light, Tr. Roy. Soc. Edinburgh 1874, pp. 27-141.

3. Granit, R.: Sensory Mechanisms of the Retina, London, Oxford University Press, 1947.

4. Jacobson, J. H., and O'Brien, J. M.: Electroretinography: Clinical Survey, Am. J. Ophth. **35**:1346, 1952.

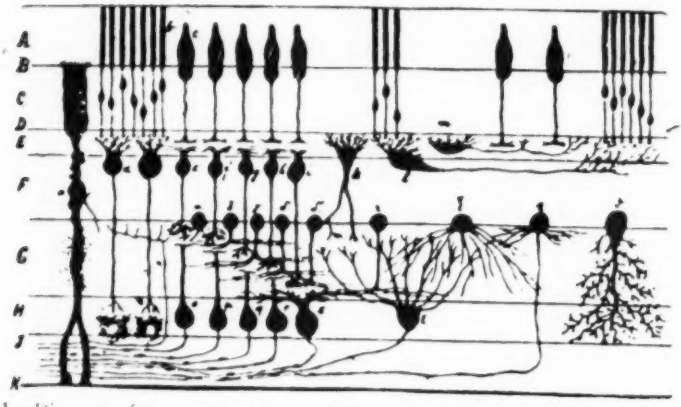


Fig. 1.—Diagram of nervous structures of the vertebrate retina. From Szymonowicz, L.: Lehrbuch der Histologie und der mikroskopischen Anatomie, Ed. 4, Leipzig, C. Kabitzsch, 1921.

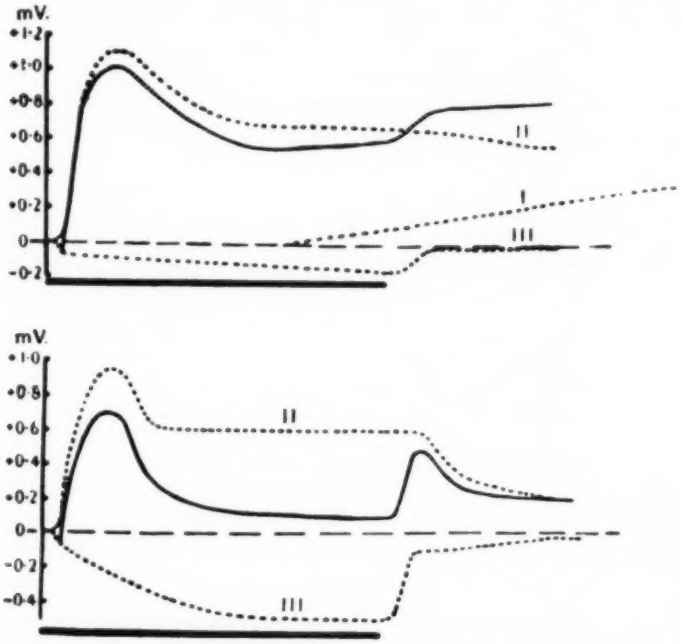


Fig. 2.—The upper electroretinogram was obtained from a dark-adapted eye. For the lower one the eye was light-adapted. In the upper curve, process I, responsible for the c wave, was present. In the lower curve it was absent. From Granit, R., and Riddell, L.: Electrical Responses of Light- and Dark-Adapted Frog's Eyes to Rhythmic and Continuous Stimuli, J. Physiol. **81**:1-28, 1934.

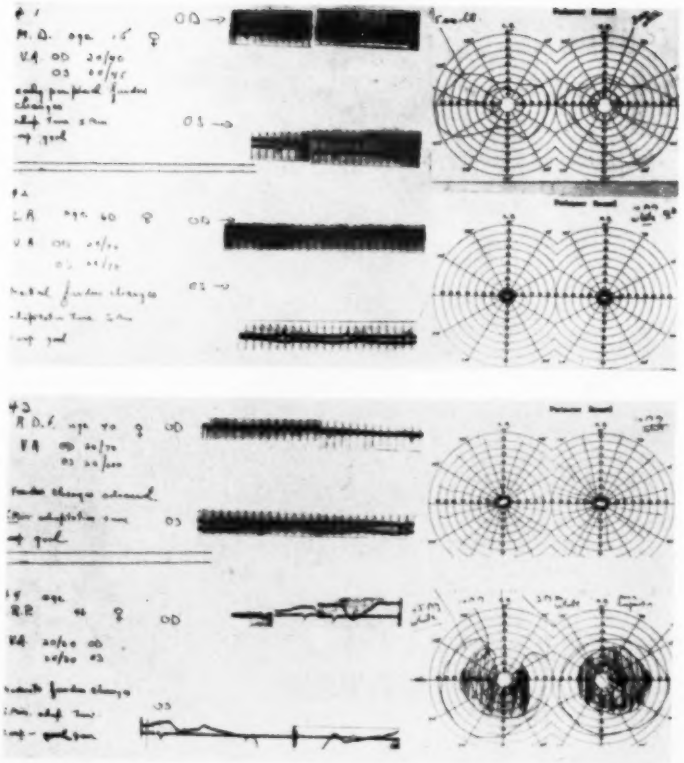

Fig. 3.—Visual acuities, adaptation times, electroretinograms, and field studies for Patients 1 and 2 (above) and Patients 3 and 4 (below).

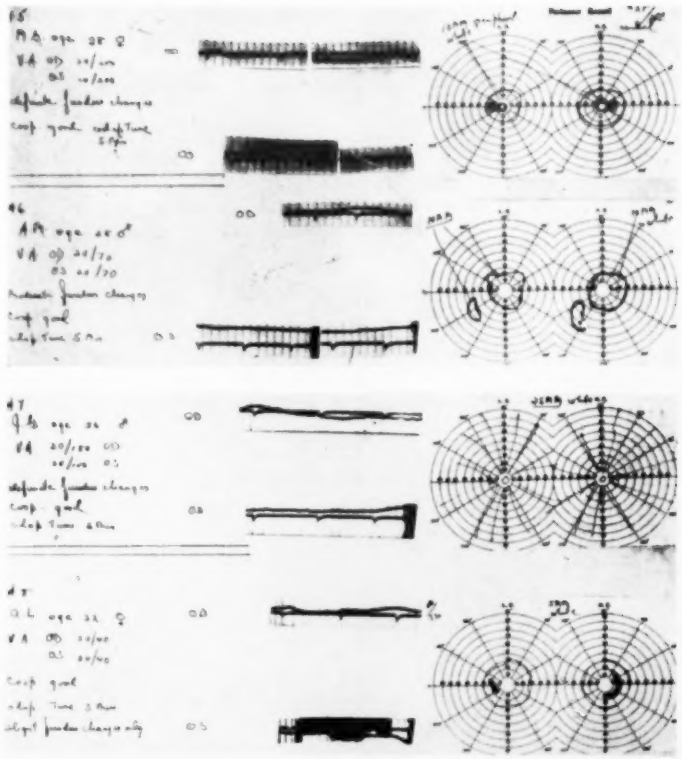

Fig. 4.—Visual acuities, adaptation times, electroretinograms, and field studies for Patients 5 and 6 (above) and Patients 7 and 8 (below).

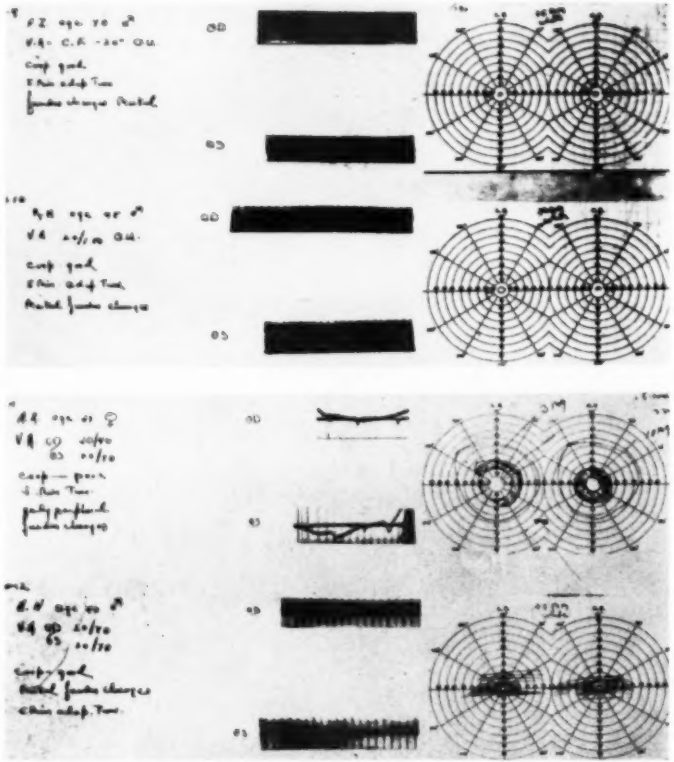

Fig. 5.—Visual acuities, adaptation times, electroretinograms, and field studies for Patients 9 and 10 (above) and Patients 11 and 12 (below).

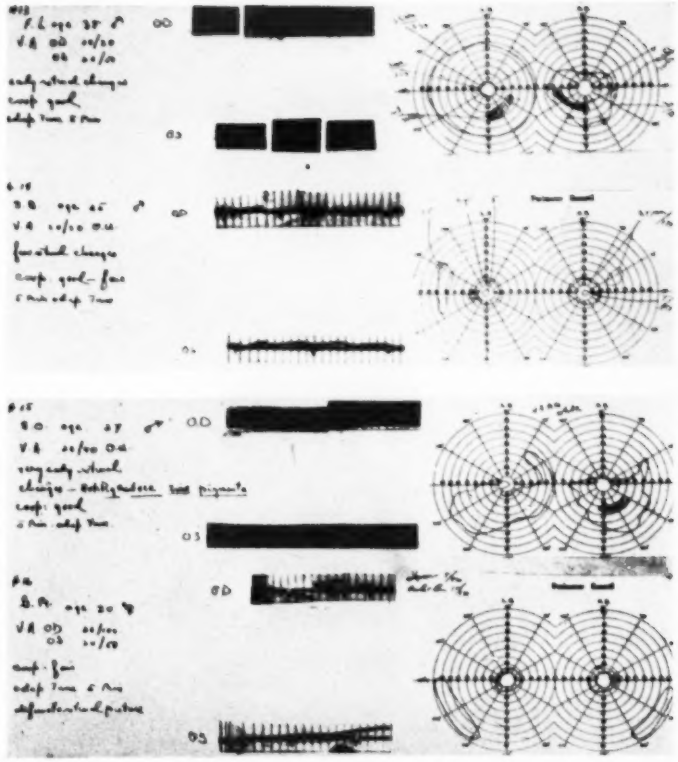

Fig. 6.—Visual acuities, adaptation times, electroretinograms, and visual fields for Patients 13 and 14 (above) and Patients 15 and 16 (below).

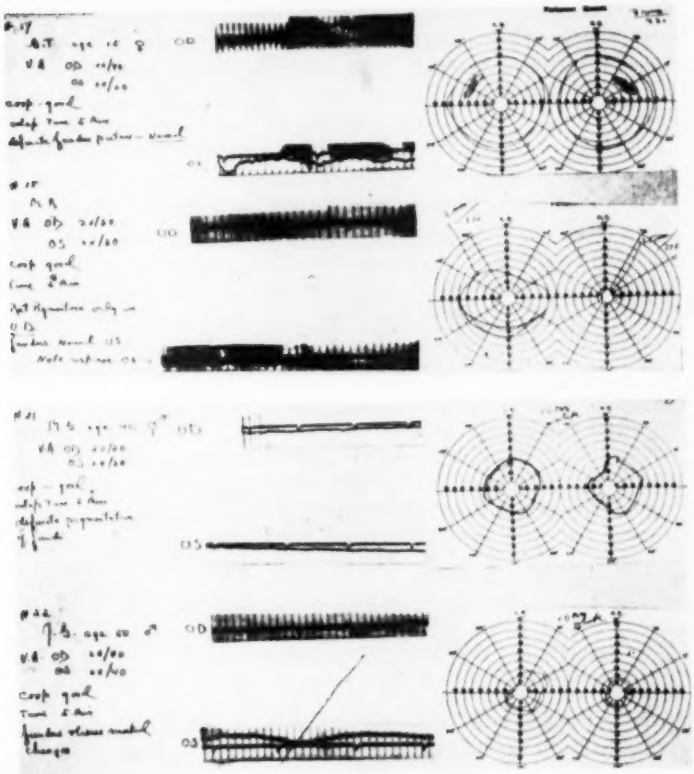

Fig. 7.—Visual acuities, adaptation times, electroretinograms, and field studies for Patients 17 and 18 (above) and Patients 21 and 22 (below).

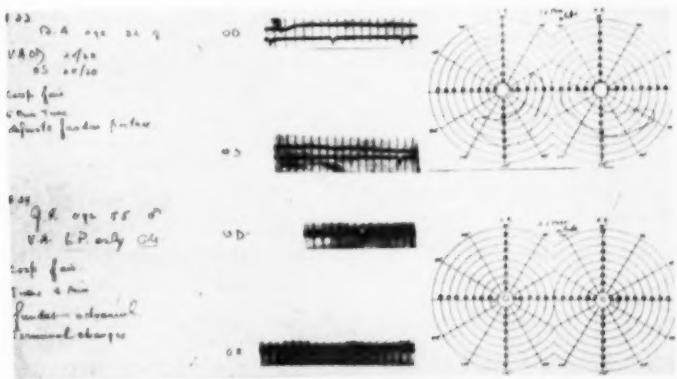

Fig. 8.—Visual acuities, adaptation times, electroretinograms, and field studies for Patients 23 and 24.

In relation to the visual chain, mention should be made of the outstanding characteristic of convergence in the vertebrate retina. By this is meant that a single ganglion cell is usually connected to more than one bipolar cell, which, in turn, is connected to more than one receptor (usually a rod). Thus, it will be seen that there are many rods in any given retinal area all connected with a single final common pathway. This effect of intercellular connection is further amplified by the two synaptic layers, namely, the amacrine and the horizontal cells. These layers, in turn, connect the retinal cells (chiefly the bipolars) horizontally, an arrangement which, when considered along with the vertical convergence present, provides for the extreme ramifications of any given retinal area. Obviously, then, it is possible for some complete connection throughout the entire retina to exist by virtue of the aforesaid vertical and horizontal synapses.

The vertebrate electroretinogram consists of four main components, as follows: (1) a small negative (a) wave; (2) a large positive (b) wave, which is the chief component of the human electroretinogram; (3) a positive (c) wave, of lower height and smaller gradient than the b-wave; (4) the "off" effects (b-wave).

For clinical work the b-wave is the most significant, since it shows greater changes when studied from many aspects, such as disease and state of adaptation. It is thought by Granit [5] that the electric wave originates in the bipolar layer and expresses activity of the synaptic retinal layers. For further details concerning electroretinography, the reader is referred to the previously mentioned writings of Granit [3] and Karpe.[6]

## METHODS AND MATERIALS

A series of patients with pigmentary degeneration of the retina formed the basis of this investigation. Twenty-four patients (48 eyes) were examined and the results tabulated. Careful screening resulted in the presentation of only such cases as are now recognized as instances of primary pigmentary degeneration. The cases were studied from the following aspects:

1. Visual acuities. Both corrected and uncorrected acuities were taken in each case.

2. Field studies. We used a standard perimeter at 35-cm. target distance. Central-field studies were not carried out.

3. Electroretinographic studies. Karpe's apparatus was used in each instance.

4. Retinal photographs. These were executed in seven cases only, the problem of securing the patients for photographs being impossible in the rest of the cases.

The series represented nearly every aspect of the disease, as will be apparent from the slides. A wide variety of ages, visual acuities, and field changes was presented. It will be of interest that no matter what the stage of the disease, the electric response was similar in all instances. The clinical material is presented in Figures 3 to 8.

## RESULTS

From the accompanying tracings, it will be seen that in all instances the electroretinogram showed a lack of response to the light stimulus. Moreover, this lack of response was the same no matter what stage or degree of development the disease showed and was the same for all the 48 eyes thus examined.

## COMMENT

It is now generally believed that the initial lesion of pigmentary degeneration is in the visual receptor cells. The disease begins equatorially and spreads to involve

5. Karpe, G.: The Basis of Clinical Electroretinography, Acta ophth., Supp. 24, 1945.

6. Karpe,[5] p. 15.

the entire retina. Since the equatorial area of the retina is predominantly composed of rods, it follows that the rods are primarily affected. Whether this is due to the nature of the disease itself or to the rods being more numerous at the equator is not presently known. The receptor cells having primarily been attacked, involvement proceeds until the ganglion cells alone remain in the visual chain. Proliferation of neuroglia and pigmentary migration follow in turn, producing the characteristic visual symptoms resulting in the name night blindness.

Of special interest in this regard is the fact that the electroretinograms seen in this series are essentially due to rod rather than to cone activity. This is evident from the effect of dark adaptation on the tracings, and the matter has been fully discussed by both Granit and Karpe in their monographs. In addition, it is assumed that the potentials producing the retinograms arise in the synaptic layers of the retina.[7] Consequently, since the synaptic layers are intimately involved in the production of the retinogram, and since the rods are connected with many other rods by these synapses, the absence of any tracing whatsoever is significant. From this study it must be concluded that there is a definite alteration of the potential in the synaptic layers, causing complete absence of any rod activity comparable to that of a normal eye. Just when this change occurs is presently not known, but it could be seen in the earliest-obtained tracings of this series.

Another problem arising from this study is the involvement of the cone receptors. Are they affected primarily or only because of subsequent atrophic changes throughout the entire retina? We shall seek the answer to this question by separating the rod from the cone retinogram. The results of these studies should yield information of some interest in the attack on this terrible affliction.

SUMMARY

A series of 24 patients upon whom electroretinograms were taken in conjunction with other clinical studies are presented. The method of taking the tracings, with a brief outline of the physiology of the electroretinograms, is given. The results are presented and discussed from the standpoint of the origin of the disease and the absence of any tracings even in the earliest stages of the disease. We plan further studies along these lines.

ABSTRACT OF DISCUSSION

DR. FRANCIS H. ADLER, Philadelphia: What part of the retina did Dr. O'Brien stimulate after preliminary exposure in order to obtain his electroretinograms?

The electroretinogram, of course, is a complex series of waves having its origin (or the various components having their origin) in different portions of the visual apparatus. The b-wave is considered to originate in the rod mechanism. If the author chose to employ a portion of the retina which was still functioning and still had cones, he should have obtained those portions of the electroretinogram which represent other than the rod mechanism. It seems strange that instead he got no response whatsoever.

7. Granit, R.: Sensory Mechanisms of the Retina, London, Oxford University Press, 1947, Chap. 3.

# BILATERAL SUPERIOR OBLIQUE PARALYSIS

MARTIN J. URIST, M.D.
SOUTH HAVEN, MICH.

BILATERAL paralysis of the superior oblique muscle may be congenital or acquired. The typical symptoms of bilateral superior oblique paralysis following trauma to the skull have been described by Bielschowsky,[1] Adler,[2] and Walsh.[3] The findings are characteristic in that there are diplopia in the lower fields of gaze and fusion in the upper fields. The head is bent, with the chin on the chest, so that the eyes will look into the upper field of single vision. On looking down and to the right there is left hypertropia with diplopia, and on looking down and to the left there is right hypertropia with diplopia. Adler [2] charted the diplopia fields for this condition, which showed the left image lower on gaze to the right and the right image lower on gaze to the left. In the upper field the images came together. Bielschowsky [1] figured the findings with the Helmholtz head-tilting apparatus. On tilt to the left the image of the left eye was lower and intorted; on tilt to the right the right image was lower and intorted.

It is the purpose of this paper to report two cases of congenital bilateral superior oblique paralysis in which the head tilt and presenting symptoms were those of a unilateral superior oblique paralysis.

## REPORT OF CASES

CASE 1.—H. A., aged 9 years, came to the Infirmary on Aug. 17, 1947, with the history of a head tilt to the right and occasional diplopia since birth. Birth was with forceps delivery after prolonged labor.

With atropine cycloplegia, refraction was as follows:

O.D.: + 0.50 sph. = 20/30
O.S.: + 0.50 sph. = 20/30

Preoperative examination (Fig. 1) revealed torticollis to the right with stereopsis. When the head was straightened, the patient complained of vertical diplopia, and left hypertropia was found. Tilting of the head to the left induced a pronounced elevation of the left eye (Bielschowsky's sign). In dextroversion the left eye was elevated in all positions. In levoversion the eyes were on the same level in all positions. On gaze straight up and straight down, the left

From the Department of Ophthalmology of the Illinois Eye and Ear Infirmary, University of Illinois College of Medicine.

1. Bielschowsky, A.: Lectures on Motor Anomalies, Dartmouth College Publications, Hanover, N. H., 1940, p. 74.

2. Adler, F. H.: Some Confusing Factors in the Diagnosis of Paralysis of the Vertically Acting Muscles: Jackson Memorial Lecture, Am. J. Ophth. **1**:387 (April) 1948.

3. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, p. 264

eye was higher. The near point of convergence was 65 mm. Cover measurements were as follows: for distance, 3△ of esophoria and 5△ of left hyperphoria; for near, 4△ of left hyperphoria.

Measurements in the cardinal positions were as follows:

| | | | | |
|---|---|---|---|---|
| | X 16<br>LH20 | X 20<br>LH16 | X 10 | |
| Right | LH 7 | LH 4 | E 3 | Left |
| | E 14<br>LH 3 | E 8<br>LH 3 | E 12<br>LH 2 | |

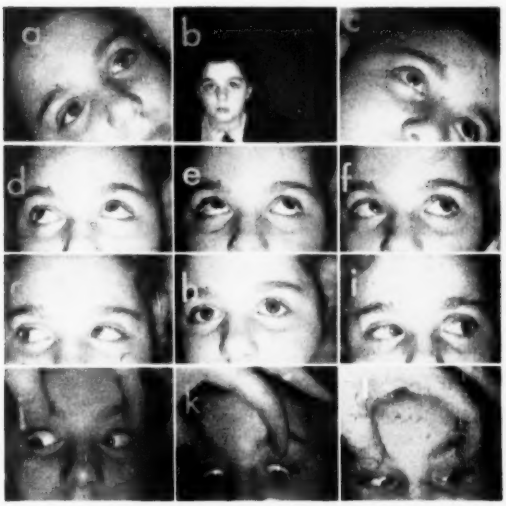


Fig. 1 (Case 1).—Preoperative photographs: (*a*) head tilted to right, eyes on same level, no diplopia; (*b*) torticollis constantly present (not clearly shown on photograph), no diplopia; (*c*) head tilted to left, left eye elevated (Bielschowsky sign); (*d*) marked elevation of left eye on gaze up and to right; (*e*) slight divergence and elevation of left eye on straight upward gaze; (*f*) eyes on same level on gaze up and to left; (*g*) marked elevation of left eye on dextroversion; (*h*) left hypertropia (and diplopia) when head is straightened; (*i*) eyes level on levoversion; (*j*) limitation of left eye on gaze down and to right; (*k*) slight limitation of left eye on straight downward gaze; (*l*) eyes on same level on gaze down and to left.

Cover measurements were much less on looking down and to the right (LH3) than up and to the right (LH20). This is not typical of left superior oblique paralysis and most likely was due to the marked overaction of the right inferior oblique (direct antagonist). Actually, the photographs show a much greater left hypertropia than 3△ on looking down and to the right (Fig. 1*j*). This may be because the elevation of the left eye was present in such an extremely adducted position that it could not be measured.

A diagnosis of paralysis of the left superior oblique with overaction of the left inferior oblique was made largely on the basis of the typical torticollis, Bielschowsky's head-tilting sign, and the limitation of the left eye in dextrodepression.

Surgical treatment, on Aug. 17, consisted of a 10-mm. recession of the left inferior oblique.

Postoperative examination, two months after surgical intervention (Fig. 2) revealed, surprisingly, that the patient then had a torticollis to the left. When the head was straightened, she complained of vertical diplopia and a right hypertropia was present. In levoversion the right eye was higher than the left in all positions, while the eyes remained on the same level in all positions in dextroversion. In looking straight up and straight down the right eye was higher. The convergence near point was 85 mm.

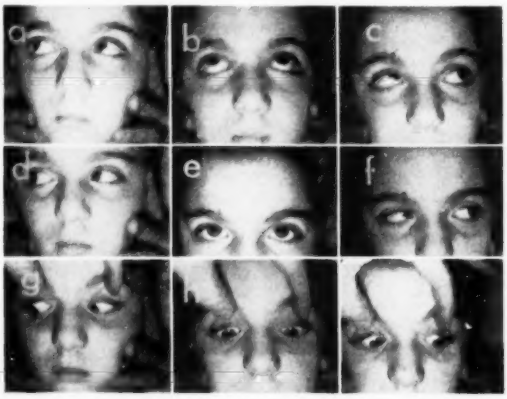


Fig. 2 (Case 1).—Postoperative photographs, two months after 10-mm. recession of left inferior oblique: (*a*) eyes on same level up and to right; (*b*) some divergence and elevation of right eye on straight upward gaze; (*c*) marked elevation of right eye on gaze up and to left; (*d*) slight elevation in adduction of left eye on dextroversion; (*e*) right hypertropia (and diplopia) when head is held straight; (*f*) marked elevation in adduction of right eye on levoversion; (*g*) eyes on same level on gaze down and to right; (*h*) eyes on same level looking straight down; (*i*) slight limitation of right eye on gaze down and to left. Compare eyes in this Figure with condition shown in Figure 1.

Cover measurements showed 3△ of right hyperphoria for distance and 2△ of right hyperphoria for near. Measurements in the cardinal positions were as follows:

| | | | | |
|---|---|---|---|---|
| | X 16 | X 16<br>RH 6 | X 16<br>RH15 | |
| Right | X 9 | RH 2 | RH12 | Left |
| | 0 | RH 2 | E 8<br>RH 8 | |

A diagnosis of right superior oblique paralysis and overaction of the right inferior oblique was made at this time.

A second operation, on Aug. 10, 1948, was a 10-mm. recession of the right inferior oblique.

Postoperative examination, 2½ years after the second operation, (Fig. 3) revealed that the eyes were straight, with no torticollis, the patient had third-grade fusion, and the convergence

near point was 50 mm. Cover measurements were 2△ of exophoria for distance, and, for near, 14△ of exophoria and 3△ of either left hyperphoria or right hyperphoria, depending on which eye was measured. Measurements in the cardinal positions were as follows:

| | | | | |
|---|---|---|---|---|
| | X 20<br>LH 2 | X 25 | X 20<br>RH 5 | |
| Right | X 12<br>LH 2 | X 14<br>LH 3<br>RH 3 | X 5 | Left |
| | E 27<br>LH 6 | X 5 | 0 | |

CASE 2.—D. B., aged 5 years, came to the Infirmary on July 10, 1948, with the history of the right eye shooting up at times, accompanied by diplopia. A head tilt to the left had been present since infancy.

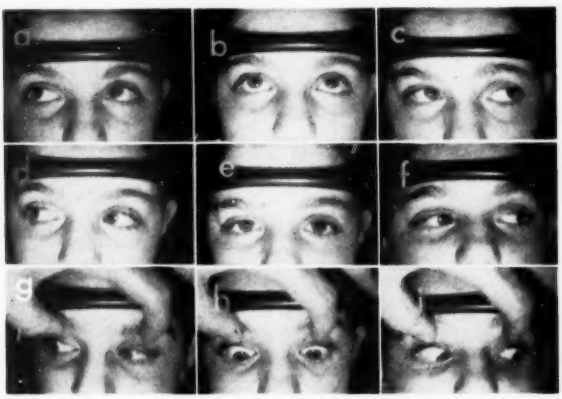


Fig. 3 (Case 1).—Postoperative photographs, 2½ years after second operation, consisting of 10-mm. recession of right inferior oblique: (*a*) slight elevation of left eye on gaze up and to right; (*b*) eyes on same level on gaze straight up; (*c*) eyes on same level on gaze up and to left; (*d*) eyes on same level on dextroversion; (*e*) eyes level (no hypertropia) when head is held erect; (*f*) eyes on same level on levoversion; (*g*) apparent right hypertropia, probably an artifact (clinically eyes were on same level on gaze down and to right); (*h* and *i*) eyes on same level on gaze straight down and on gaze down and to the left.

With atropine cycloplegia, refraction was as follows:

O.D.: + 0.37 ⌒ + 0.25 cyl., ax 120 = 20/30
O.S.: + 1.00 ⌒ + 0.25 cyl., ax 70 = 20/50

Examination (Fig. 4) revealed torticollis to the left. When the head was straightened, diplopia was complained of and right hypertropia was visible. When the head was tilted to the right, the right eye deviated up markedly (Bielschowsky's sign). In levoversion the right eye was markedly elevated in all positions. In dextroversion the left eye was slightly elevated in all positions. The elevation of the left eye is shown well in the photographs (Fig. 4, *d*, *g*, *j*). It appeared to be much less clinical and was thought to be insignificant, especially since the cover measurements showed right hyperphoria on gaze to the right in all positions (see measurements below). On looking straight up and straight down the right eye was higher. The

near point of convergence was 60 mm. On the major amblyoscope third-grade fusion was found at the objective angle. Cover measurements were 3△ of right hyperphoria and 5△ of exophoria and 12△ of right hyperphoria for near.

Measurements in the cardinal positions were as follows:

| | | | | |
|---|---|---|---|---|
| | RH 4 | X 4<br>RH 8 | RH18 | |
| Right | RH 3 | X' 5<br>RH12 | RH22 | Left |
| | RH 4 | RH12 | RH25 | |

A diagnosis of right superior oblique paralysis with overaction of the right inferior oblique was made.

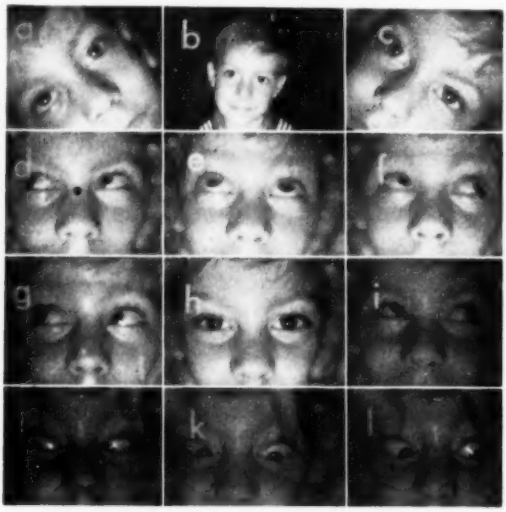


Fig. 4 (Case 2).—Preoperative photographs: (*a*) head tilted to right, right eye elevated, vertical diplopia (Bielschowsky sign); (*b*) torticollis to left, maintained constantly, with stereopsis; (*c*) head tilted to left, eyes on same level, no diplopia; (*d*) slight elevation of left eye on gaze up and to right; (*e*) slight elevation of right eye on gaze straight up; (*f*) marked elevation of right eye on gaze up and to left; (*g*) slight elevation of left eye on dextroversion; (*h*) diplopia indicating right hypertropia when head is held straight; (*i*) marked elevation of right eye in adduction; (*j*) slight limitation of left eye down and to right; (*k*) lag of right eye on gaze straight down; (*l*) limitation of right eye down and to left.

Operation, on July 28, 1948, consisted of a 12-mm. recession of the right inferior oblique and a 3-mm. recession of the right lateral rectus.

Postoperative examination, six months later (Fig. 5), revealed that the patient then had a torticollis to the right. When the head was straightened, left hypertropia and diplopia became manifest. Tilting the head to the left caused the left eye to become markedly elevated (Bielschowsky's sign). In dextroversion the left eye was elevated in all positions; in levoversion the eyes appeared on the same level. On gaze straight up and down the left eye was higher. On the major amblyoscope stereopsis was found at the objective angle. The convergence near point was 30 mm.

Cover measurements revealed orthophoria for distance and, for near, esophoria of 3△ and left hyperphoria of 4△. In the cardinal positions of gaze the findings were as follows:

| | | | | |
|---|---|---|---|---|
| | E 4<br>LH14 | E 2<br>LH 9 | LH 5 | |
| Right | 0 | E' 3<br>LH 4 | 0 | Left |
| | E 7 | E 7 | E 5 | |

After this unexpected operative result, the preoperative photographs were reexamined (an advantage in taking routine photographs). At this time what before operation had been believed to be an insignificant elevation of the left eye in dextroversion assumed diagnostic importance

Fig. 5 (Case 2).—Postoperative photographs six months after 12-mm. recession of right inferior oblique and 3-mm. recession of left lateral rectus: (*a*) head tilt to right, eyes on same level (compare Fig. 4*a*); (*b*) torticollis to right, constantly present, with stereopsis and no diplopia; (*c*) head tilted to left, elevation of left eye with vertical diplopia (Bielschowsky sign); (*d*) marked elevation of left eye on gaze up and to right; (*e*) elevation of left eye on gaze straight up; (*f*) eyes on same level on gaze up and to left; (*g*) elevation of left eye in adduction; (*h*) diplopia indicating left hypertropia when head is held straight; (*i*) eyes level on levoversion; (*j*) slight lag of left eye down and to right; (*k*) left eye slightly higher than right on gaze straight down; (*l*) eyes on same level on gaze down and to left. Compare all poses with those in Figure 4.

It was now thought that this elevation was a manifestation of the underlying left superior oblique paresis with overaction of the left inferior oblique and that more attention should have been paid to it before operation. Moreover, an attempt should have been made to elicit left hypertropia by perhaps more concentration on the right field and by many repeated measurements. However, it may be possible that the elevation of the left eye was found only in the extreme adducted position, in which it could not be measured. It may be, also, that in these cases of bilateral paresis, in order for a unilateral paresis to be simulated, the more pronounced paresis must become very dominant. This dominance may be manifested by its being possible

to measure only a unilateral hypertropia in nearly all fields. After operation the left hypertropia was found on gaze up and to the right, on gaze straight up, and on gaze up and to the left in this case, while in Case 1 preoperative measurements showed a left hyperphoria on gaze down and to the right, straight down, and down and to the left.

A diagnosis of left superior oblique paralysis and overaction of the left inferior oblique was then made.

The second operation, on Feb. 20, 1949, was a 6-mm. recession of the left inferior oblique.

Postoperative examination, on July 25, 1951, 2½ years after operation (Fig. 6), revealed no torticollis and no diplopia on looking straight ahead. In dextroversion and in dextroelevation the left eye was slightly elevated. The near point of convergence was 40 mm.; third-grade fusion

Fig. 6 (Case 2).—Postoperative photographs, 2½ years after second operation, consisting of 6-mm. recession of left inferior oblique: (*a*) eyes on same level with head tilted to right (vertical diplopia, with right image lower); (*b*) no torticollis and no diplopia (stereopsis); (*c*) eyes on same level with head tilted to left (vertical diplopia, with left image lower); (*d*) some elevation of left eye on gaze up and to right; (*e*) eyes on same level on gaze straight up; (*f*) eyes on same level on gaze up and to left; (*g*) slight elevation in adduction of left eye on dextroversion; (*h*) eyes on same level looking straight ahead, no diplopia; (*i*) eyes on same level on levoversion; (*j*) slight elevation of left eye on gaze down and to right; (*k*) eyes on same level on downward gaze; (*l*) eyes on same level on gaze down and to left.

was present at 0 on the major amblyoscope. Cover measurements were 3△ of esophoria for distance and 6△ of esophoria for near. Measurements in the cardinal positions were as follows:

| | | | | |
|---|---|---|---|---|
| | X 6<br>LH 4 | 0 | 0 | |
| Right | E 6<br>LH 2 | E 6 | 0 | Left |
| | E 12 | E 10 | E 7 | |

Most interesting was the finding that when the patient's head was tilted to the left he had vertical diplopia, indicating left hypertropia. On tilting the head to the

right, he had vertical diplopia, indicating right hypertropia. No upshoot of the eyes, however, could be seen. The bilateral diplopia in this case served a useful purpose after operation in maintaining the head straight.

## COMMENT

The bilaterality of the paresis of the superior oblique in these cases became grossly manifest after the overaction of the more involved inferior oblique was corrected surgically. Knowledge that this occurs is of clinical importance, for when a child with apparently unilateral paresis of the superior oblique is operated on the parents and surgeon may be surprised, as we were, when the patient manifests hypertropia and torticollis the opposite of that which was present before operation. This may lead the surgeon to feel that he has overcorrected the original condition and to redo what has been done. Townes [4] described a case of this type in which, after multiple operations, he finally concluded that the original condition was a bilateral superior oblique paralysis.

The use of torticollis in these cases enables the patient to have singular binocular vision in ordinary use of the eyes. The head-tilt test of Bielschowsky was positive in the present cases and indicated a paresis of the superior oblique. The pathologic physiology of these findings in cases of superior oblique paralysis was explained by Bielschowsky.[1] He stated:

> Let it be supposed that in a case of right trochlear-nerve palsy the head is tilted toward the right shoulder. From this will arise a vestibular excitation of those muscles that are able to produce a parallel rotary movement of the eyes to the left [levocycloversion]. This movement is produced in the left eye by the two inferior muscles, and in the right eye by the two superior muscles. The paralyzed right superior oblique muscle can no longer compensate the elevating and adducting component of the right superior rectus, from which a vertical and a lateral deviation of the right visual line must result, whereas in a normal person both the visual axes would be stationary. And what will happen if the head of the patient with the paretic right superior oblique muscle is tilted toward the left side? Both inferior muscles of the right eye and the superior muscles of the left eye receive the vestibular innervation to rotate the eye around the visual axis to the right [dextrocycloversion]. This movement can be performed without the coöperation of the paretic muscle; hence no deviation of the visual axis will result. As mentioned before, the more the sound muscles are burdened the more favored will be the paretic muscle. Now one can understand the reason for the habitual tilting of the head that is observed in so many cases of trochlear-nerve palsy. If the head is tilted toward the shoulder of the sound side, a coöperation of the superior oblique muscle is not called for, so that binocular single vision is obtained. . . . .
>
> I have not yet been able to find out why the tilting is of no use in palsies of the vertical recti, although these muscles help to bring about rotation of the eyes [cycloversion] around the visual axes necessitated by tilting the head toward the opposite side. According to my experience, paresis of the superior or inferior oblique is in all cases at the bottom of ocular torticollis, provided that only by this posture can binocular single vision be obtained.

Adler [5] explained the minor importance of the head tilt in paralysis of the vertical rectus muscles on the much greater torsional action of the oblique muscles as compared with that of the vertical rectus muscles. He stated:

> Tilting the head on the right shoulder sends an increase of tonic impulses to those muscles of the right eye which cause intorsion, i. e., the right superior oblique and the right superior rectus.

4. Townes, C. D.: Surgical Treatment of Heterophoria, Tr. Am. Acad. Ophth. **49**:338 (July-Aug.) 1945.

5. Adler, F. H.: Physiology of the Eye: Clinical Application, C. V. Mosby Company, St. Louis, 1950, p. 407.

Normally, these two muscles, contracting together by just the right amount, produce nothing but intorsion, as their elevating and depressing actions on the globe neutralize one another. If the right superior oblique is paralyzed, the superior rectus works alone and produces some intorsion, but also a marked elevation of the globe, since its upward movement is no longer prevented by the downward pull of the superior oblique muscle.

If the superior rectus is paralyzed and the head tilted on the shoulder of the same side, no upward movement of the globe is produced, since the muscle which is most effective in producing intorsion is still intact (superior oblique). The necessary amount of intorsion is produced by this muscle practically alone, the superior rectus being contracted simultaneously merely to counterbalance the slight depressing action of the superior oblique as it contracts in the primary position. If any vertical movement of the globe results from this tilting procedure, it will be a slight downward movement of the eye, due to the unopposed action of the superior oblique.

Another component is present which I believe to be of importance in explaining why torticollis is more commonly found in cases of superior oblique paralysis than in cases of superior rectus paralysis. The explanation follows:

When the eyes are in primary position and fixing a small object and the head is tilted, certain eye movements normally occur along with cyclotorsion. When the head is tilted to the right shoulder, the right orbit is displaced below the horizontal and to the right. This causes the right eye to move up and in to maintain fixation. The left eye will move out and slightly vertically, depending on the direction of face rotation. In a case of right superior oblique paralysis, when the head is tilted to the right shoulder, the right eye may become markedly elevated (Bielschowsky's sign). This may be explained as due to the summation of the following two elevating effects: (1) elevation due to overaction of the right superior rectus muscle because of the unbalanced cyclotorsional movements, as explained above, and (2) elevation due to overaction of the right inferior oblique, since the right eye has moved up and in, into the field of the greatest elevating action of this muscle. In Case 2 overaction of the inferior oblique was corrected surgically, and the pronounced upshoot on tilting the head (Bielschowsky's sign)disappeared. Vertical diplopia was still present with the head tilted to either side, however, owing to the remaining uncorrected paresis of the superior obliques and the remaining elevating effect of the superior rectus (compensatory torsional component).

In a case of right superior rectus paralysis the right eye may be depressed only slightly when the head is tilted to the right. This is because (1) the right superior oblique can rotate the eye well (Adler[5]) and (2) the right eye moves up and in, as explained in normal eyes, and away from the field of a possibly overacting inferior rectus.

These principles will apply in accounting for the efficacy of torticollis in case of paresis of the superior oblique or of the superior rectus. In a case of right superior oblique paralysis the torticollis to the left will be very effective because (1) the paretic superior oblique takes no part in the dextrocyclotorsion of the right eye and (2) the right eye is abducted, so that it is taken out of the field of a possibly overacting inferior oblique. In the case of right superior rectus paralysis the torticollis to the left will not work as well, since, although the superior rectus takes no part in the dextrocyclotorsion, the eye, by moving out, moves into the field of a usually overacting inferior rectus (direct antagonist).

SUMMARY

Two cases of congenital bilateral superior oblique paresis with bilateral overaction of the inferior oblique muscle are presented. Both cases were unusual in that the initial findings were typical of a unilateral superior oblique paresis, including torticollis and the diagnostic Bielschowsky head-tilting sign. Only after recession of the initial overacting inferior oblique did the paresis of the superior oblique and the overaction of the inferior oblique of the other eye become manifest.

An explanation is added to the classic one for the greater efficacy and frequency of torticollis in superior oblique paresis than in superior rectus paresis. This takes into consideration the movement of the eyes away from or into the field of the greatest action of a possibly overacting direct antagonist when the head is tilted.

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# HONEYCOMB COLLOID DEGENERATION OF THE RETINA

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AND
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SEVEN cases of colloid degeneration of the retina recently observed in three generations of the same family are reported. The condition described is probably the same as the abiotrophy reported by Doyne as "honeycomb colloid choroiditis."[1] Because none of the previous reports in the available literature concern American families, it seemed worth while to present the present review, together with a report of our cases.

## HISTORICAL REVIEW

The first reference in the literature to a familial occurrence of colloid degeneration of the retina was made in 1876 by Hutchinson,[2] who observed that three of Warren Tay's original cases of "guttate choroiditis" were of siblings. It remained for Doyne,[3] however, to describe the condition as a separate entity in 1899, when he observed the disease in four members of one family. In 1910 he reported an additional family of four, at which time Butler [4] also reported a family with similar disturbances. Since then, other cases with a family history have been reported by Mould [5] and Tree.[6] All the foregoing cases were found in families in central England.

In 1936, Malbrán and Adrogué,[7] in Argentina, reported one case in which the disease was not familial. Pajtas,[8] in 1950, reported a family in Czechoslovakia in which a son and daughter had ophthalmoscopic signs of colloid degeneration of the retina and a history of poor vision was obtained in the father and three ancestors.

Doyne observed that the disease was hereditary and noted its onset as early as 20 years of age, but more commonly at about 40. He described circular whitish patches of a honeycomb appearance affecting the disk-macula area bilaterally. These increased in size and number in middle age, when some degree of pigmentary degeneration occurred. It was noted that in old age the discrete outline of the spots producing the honeycomb appearance disappeared, the patches merging to form a

From the Department of Ophthalmology, Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine, and the Children's Hospital of Philadelphia.

1. Sorsby, A.: Tr. Ophth. Soc. United Kingdom **54**:160, 1934.
2. Hutchinson, J.: J. Roy. London Ophth. Rep. **8**:231, 1876.
3. Doyne, R. W.: Tr. Ophth. Soc. United Kingdom **19**:71, 1899; **30**:93, 190, 1910.
4. Butler, H.: Tr. Ophth. Soc. United Kingdom **30**:94, 1910.
5. Mould, G. T.: Tr. Ophth. Soc. United Kingdom **30**:189, 1910.
6. Tree, M.: Brit. J. Ophth. **21**:65, 1937.
7. Malbrán, J., and Adrogué, E.: Arch. oftal. Buenos Aires **11**:529, 1936.
8. Pajtas, J.: Československ. oftal. **6**:282, 1950.

homogeneous, atrophic area. The visual disturbances were not in proportion to the apparent severity of the lesions seen ophthalmoscopically except in patients with atrophic areas, in whom a progressive failure of sight occurred. Pajtas [8] reported ophthalmoscopic findings similar to those originally described by Doyne. He noted,

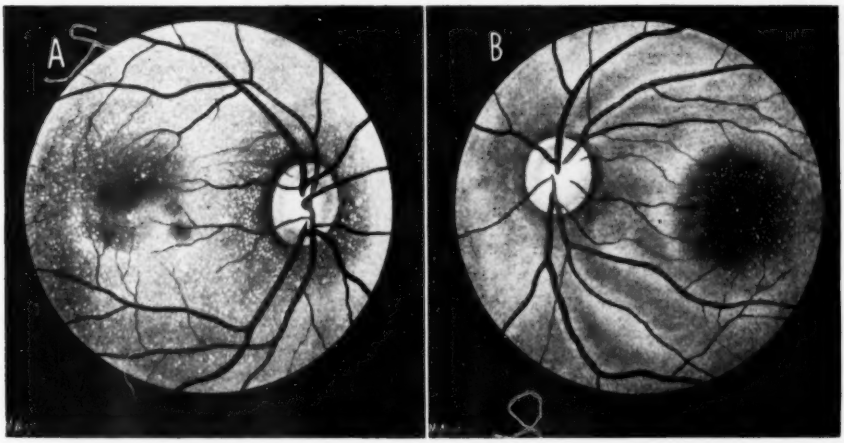


Fig. 1.—*A* (Case 6), drawing of fundus showing punctate deposits of colloid, resembling retinitis punctata albescens; *B* (Case 7), drawing of fundus illustrating deposition of colloid in macular region only, resembling Tay's guttate choroiditis.

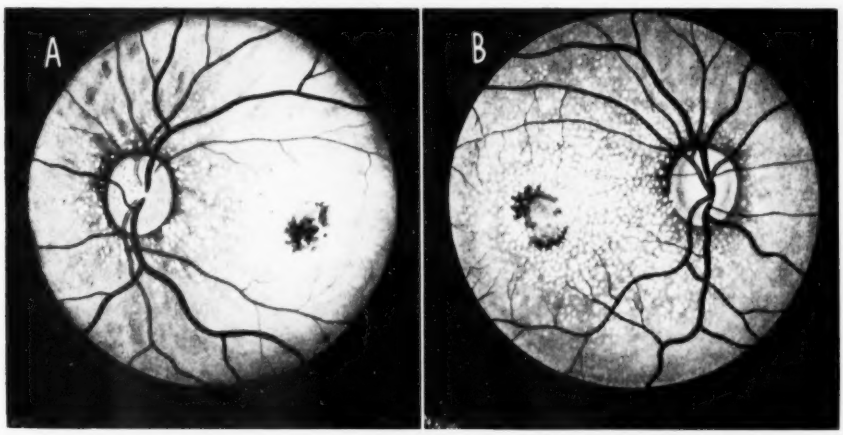


Fig. 2.—*A* (Case 1), drawing of fundus showing coalescence of colloid deposits in macular region associated with atrophy and pigment proliferation; *B* (Case 2), drawing of fundus showing coalescence of the more punctate colloid deposits into larger ones in "disk-macula" area. Pigment proliferation is seen in macular region.

however, that dark adaptation, as determined by the Birch-Hirschfeld apparatus, was much decreased.

The pathology of this condition was described by Treacher Collins,[9] who noted large plaque-like hyaline masses, similar to drüsen. Pigmentary disturbances were

9. Collins, E. T.: Ophthalmoscope **9**:537, 1913.

described in the pigment epithelium, but the retina and choroid showed no changes other than those of pressure resulting from the hyaline masses. He attributed the disease to some hereditary degeneration of the pigment epithelium.

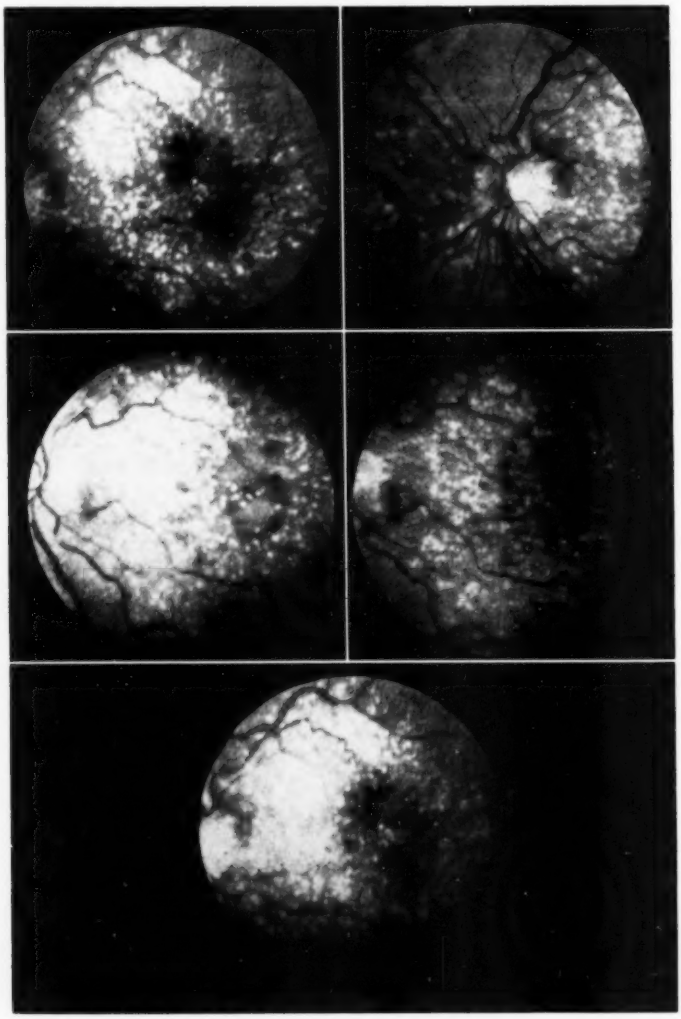

Fig. 3 (Case 2).—Retinal photographs.

## REPORT OF CASES

Seven cases of colloid degeneration of the retina are reported. In the first five cases the changes were similar to those described by Doyne in his original communication. In Case 6 the retinal picture was suggestive of retinitis punctata albescens (Fig. 1 *A*), while in Case 7 the fundus resembled Tay's guttate choroiditis (Fig. 1 *B*).

CASE 1.—T. B. Sr., a white man aged 66, came to the ophthalmology outpatient department of the Hospital of the University of Pennsylvania on Jan. 26, 1952, at our request in order that we might complete the examination of members of his family. He complained of a slowly progressive loss of vision, especially in dim illumination, for the past few years. His corrected vision was 6/22 in each eye. The results of external and slit-lamp examinations were normal. Ocular tension was 22 mm. Hg in each eye (Schiøtz). Ophthalmoscopic examination (Fig. 2*A*) revealed the same fundus picture in the two eyes. The media were clear, and the disk had good outline, color, and physiologic cupping. The vascular pattern revealed a moderate degree of arteriosclerotic change. Situated predominantly between the superior and the inferior temporal vessels were multiple small, punctate collections of colloid. These coalesced around the macula to form larger areas of degeneration. In the central region of this area atrophy and pigment proliferation were noted. The peripheral fields were within normal limits. The central fields (Fig. 5) showed central and paracentral scotomas to 3/1000 white

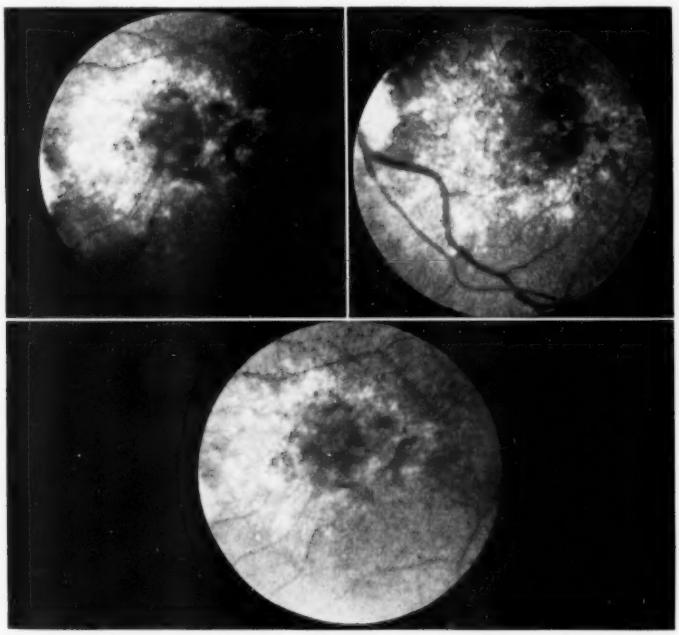

Fig. 4 (Case 5).—Retinal photographs.

CASE 2.—W. B., aged 37, the youngest son of T. B. Sr. (Case 1), was admitted to the neurosurgical service of the Hospital of the University of Pennsylvania on Jan. 20, 1952, because of a ruptured nucleus pulposus. He was referred to the ophthalmology department on Jan. 22 because of a history of progressive loss of vision during the past three years. His corrected vision was 6/22 in the right eye and 6/9— in the left eye. The results of external and slit-lamp examinations were normal. Ocular tension was 22 mm. Hg in each eye (Schiøtz). Ophthalmoscopic examination (Figs. 2*B* and 3) revealed the same fundus picture in the two eyes. The media were clear, and the disk had good color and physiologic cupping, although the margins were somewhat blurred. The vascular pattern was normal. Beneath the retinal vessels, and mainly in the area between the superior and the inferior temporal vessels, were multiple fine hard white collections of colloid. These coalesced around the macula to form larger areas of degeneration, in which pigment proliferation occurred. The peripheral fields were within normal

limits. The central field of the right eye (Fig. 6) revealed a paracentral scotoma to 2/1000 white and a centrocecal scotoma to 1/1000 white. The central field of the left eye was normal.

Case 3.—R. B., aged 43, the eldest son of T. B. Sr., came to the ophthalmology outpatient department of the Hospital of the University of Pennsylvania on Jan. 26, 1952, at our request, in order that we might complete the examination of members of his family. He had no visual complaints. His corrected vision was 6/6 in each eye. The findings on external and slit-lamp examinations were normal. Ocular tension was 22 mm. Hg in each eye (Schiøtz). Ophthalmoscopic examination of the eyes revealed similar fundus pictures. The media were clear, and the disk had good color, outline, and physiologic cupping. The vascular pattern was normal.

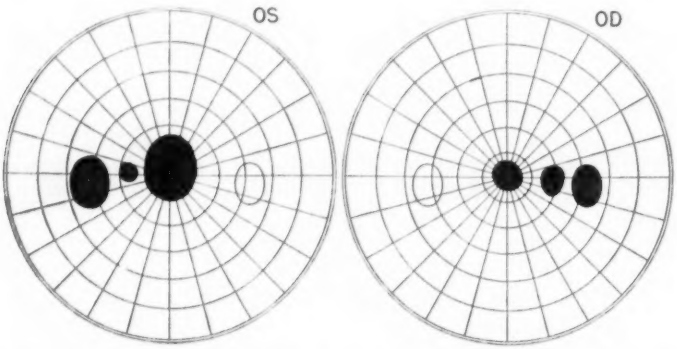


Fig. 5 (Case 1).—Central fields showing central and paracentral scotomas to 3/1000 white in both eyes.

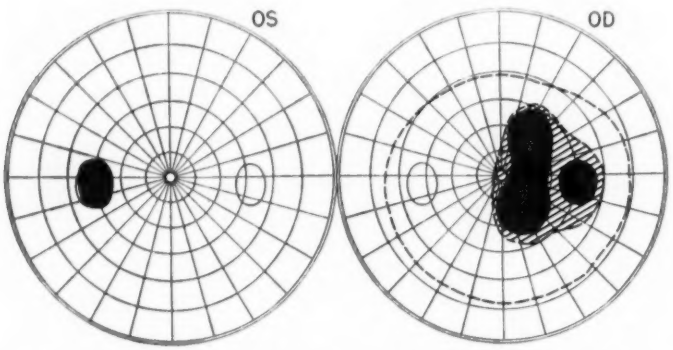


Fig. 6 (Case 2).—Central fields showing a centrocecal defect in right eye. The broken line indicates field for 1/1000 white; the solid line, field for 2/1000 white.

In the macular region were multiple small, punctate deposits of colloid, with a tendency to coalescence and pigment proliferation. In addition, some of the small colloid dots had collected to the nasal side of the disk, together with a few clumps of pigment. The peripheral fields were within normal limits. The central fields (Fig. 7) revealed a small paracentral scotoma to 1/1000 white between fixation and the blind spot in each eye.

Case 4.—M. B. H., aged 35, a daughter of T. B. Sr., came to the ophthalmology outpatient department of the Hospital of the University of Pennsylvania on Jan. 26, 1952, at our request, in order that we might complete the examination of members of her family. She had no visual complaints. Her corrected vision was 6/6 in each eye. The findings on external and slit-lamp examinations were normal. Ophthalmoscopic examination showed the same picture in the two

eyes. The media were clear, and the disk had good color and outline with a physiologic cup. The vascular pattern was normal. In the macular area, deep to the retinal vessels, were multiple small and large collections of colloid. Pigment proliferation was present, and the retina appeared atrophic in a few areas. The fovea itself was normal. The peripheral and central fields were normal.

Case 5.—E. B. C., aged 40, another daughter of T. B. Sr., came to the ophthalmology outpatient department of the Hospital of the University of Pennsylvania on Jan. 26, 1952, at our request in order that we might complete the examination of members of her family. She had no visual complaints. Her corrected vision was 6/6 in each eye. The findings on external and slit-lamp examinations were normal. Ophthalmoscopic examination (Fig. 4) of the two eyes gave similar findings. The media were clear, and the disk had good color and outline with

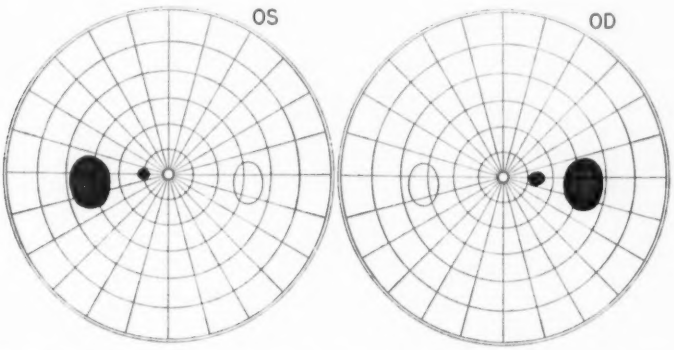


Fig. 7 (Case 3).—Central fields showing small paracentral scotomas to 1/1000 white in both eyes.

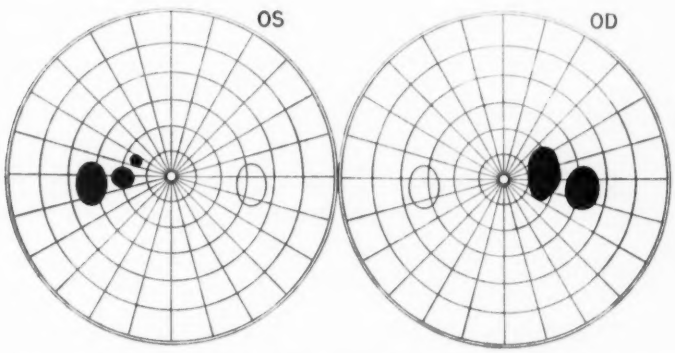


Fig. 8 (Case 5).—Central fields showing paracentral scotomas to 1/1000 white in both eyes.

a physiologic cup. The vascular pattern was normal. In the macular area multiple small and large deposits of colloid were situated deep to the retinal vessels in circinate fashion around the fovea. These colloid deposits were most conspicuous between the superior and the inferior temporal vessels, where pigment proliferation also occurred. The peripheral fields were within normal limits. The central fields (Fig. 8) showed a paracentral scotoma to 1/1000 white lying between fixation and the blind spot in the right eye and two paracentral scotomas to 1/1000 white lying between fixation and the blind spot in the left eye.

Case 6.—L. B. L., aged 23, a daughter of R. B. (Case 3) and a grand-daughter of T. B. Sr. (Case 1), came to the ophthalmology outpatient department of the Hospital of the University

of Pennsylvania on Feb. 28, 1952, at our request in order that we might complete the examination of members of her family. She complained of some difficulty in seeing distinctly at dusk but denied having night blindness. Vision was 6/6 in each eye. The results of external and slit-lamp examination were normal. Ocular tension was 22 mm. Hg in each eye (Schiøtz). The findings on ophthalmoscopic examination (Fig. 1*A*) of the two eyes were similar. The media were clear, and the disk had good outline and color with a physiologic cup. The vascular pattern was normal. Throughout the entire retina were punctate deposits of colloid, which tended to collect in the macular area. These collections were most prominent in the region between the superior and the inferior temporal vessels. No pigment proliferation was seen. The results of gross dark-adaptation tests were within normal limits. The peripheral and central fields were normal.

Case 7.—T. B. Jr., aged 20, a son of R. B. (Case 3) and a grandson of T. B. Sr. (Case 1), came to the ophthalmology outpatient department of the Hospital of the University of Pennsylvania on Feb. 28, 1952, at our request, for completion of examination of members of his family. He had no visual complaints. His vision was 6/6 in each eye. The findings on external and slit-lamp examinations were normal. The findings on ophthalmoscopic examination (Fig. 1*B*) of the two eyes were similar. The media were clear, and the disk had good outline and color with a physiologic cup. The vascular pattern was normal. The foveal area showed multiple small, fine, punctate deposits of colloid surrounding the fovea. The remainder of the retina was free of involvement. The peripheral and central fields were normal.

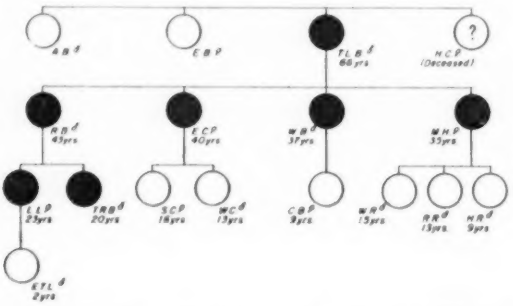


Fig. 9.—Pedigree of family investigated in this report. Black circles represent members displaying retinal pathology.

## COMMENT

The patients described in this report present a familial heredodegenerative disease of the tapetoretinal type. The disturbance is characterized by the bilateral presence of drüsen-like masses in the centrocecal area and ultimately by pigmentary degeneration with atrophy.

The members of the family which we investigated were of Irish descent and had resided in New Jersey since the grandfather (Case 1) migrated to the United States. The retinal degeneration was observed in seven members of three generations (Fig. 9). The youngest patient (Case 7) was 20 years of age, and the oldest (Case 1), 66. The incidence in the sexes was almost equal, four males and three females being affected.

Visual disturbances were noted in three patients (Cases 1, 2, and 6). The symptoms in Cases 1 and 2 consisted of decreased visual acuity, accentuated by dim illumination. In Case 6 the visual acuity was normal, but the complaints were suggestive of night blindness. Gross dark-adaptation tests, however, failed to reveal any abnormality.

The retinal changes were bilateral in all the patients and were mainly limited to the centrocecal area except in Case 6. These changes consisted of (1) a punctate deposition of colloid surrounding the fovea in a circular fashion (Case 7; Fig. 1 *B*); (2) a collection of large masses of colloid in the foveal area, associated with some pigmentary degeneration in Cases 1, 2, 3, 4, and 5 (Figs. 2, 3, and 4), and (3) atrophy in the center of the colloid masses (Case 1; Fig. 2 *A*). In Case 6 (Fig. 1 *A*) the changes were more diffuse, consisting of punctate colloid deposits distributed throughout the retina in general but displaying a tendency to collect in the macular areas. It is interesting to note that the retinal picture in Case 7 (Fig. 1 *B*), that of the youngest patient, resembled the retina in "Tay's central guttate choroiditis," a condition ordinarily seen only in senile persons.

Field changes (Figs. 5, 6, 7, and 8) consisted of central and paracentral scotomas. In four of the seven cases (1, 2, 3, and 5) these changes corresponded in position to the site of the lesions seen ophthalmoscopically.

## CONCLUSIONS

The recurrence of the disease in this family indicates that it has a hereditary basis. The Mendelian trend cannot be concluded from these observations, although it is best in accord with a single dominant gene. The possibility that the disease will appear in the unaffected members of the third generation, therefore, cannot be definitely predicted at this time.[10]

Since the disease is slowly progressive, the visual acuity usually remains good until late in life. Although there is ultimately failure of central vision, of varying degree, blindness apparently does not result.

## SUMMARY

Seven cases of colloid degeneration of the retina occurring in three generations of the same family are reported.

In five of these cases the retinal picture was characteristic of Doyne's "honeycomb colloid choroiditis." In one of these cases the process resembled retinitis punctata albescens. In another case the disease was suggestive of Tay's guttate choroiditis.

The disease is probably hereditary, with dominant Mendelian features. Although the prognosis for central vision is eventually poor, blindness apparently does not occur.

10. The Mendelian features of the disease in this family were reviewed with Dr. John O. Preer Jr., Department of Zoology, University of Pennsylvania.

# HYDROCORTISONE (COMPOUND F) IN OPHTHALMOLOGY

## Clinical and Experimental Studies

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DURING the past decade we have witnessed one of the great periods of medical history. The epoch of antibiotics and their role in infection is no less dramatic than the role of hormones and steroids in the relief of degenerative and inflammatory diseases. There have been numerous reports in the literature concerning their effectiveness in ocular disease. Leopold,[1] Woods,[2] McLean and associates,[3] and others have convincingly shown that corticotropin and cortisone have a wide spectrum of activity. One of the great advantages of cortisone in ocular therapy is that it has proved effective when used locally. Many undesirable side-effects of systemic therapy have therefore been avoided.

Hydrocortisone, or Compound F, was first described by Mason, Hoehn, and Kendall in 1938,[4] when they reported on the chemical structure of Compounds C, D, E (cortisone), F (hydrocortisone), and G, of the $C_{12}O_4$ series. Since that time approximately 28 steroids have been isolated from adrenal cortex tissue.[5] Only six of these have been shown to have important biological activity.[5] There is evidence that when the adrenal cortex is stimulated the predominant steroid secreted is hydrocortisone.[6] Under normal circumstances an appreciable quantity of corti-

From the Clinical and Research Departments of the Wills Eye Hospital.

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This study was supported by a research grant from the National Institute of Neurological Disease and Blindness, of National Institutes of Health, Public Health Service.

1. Leopold, I. H.; Purnell, J. E.; Cannon, E. J.; Steinmetz, C. G., and McDonald, P. R.: Local and Systemic Cortisone in Ocular Disease, Am. J. Ophth. **34**:361 (March) 1951.

2. Woods, A. C.: Clinical and Experimental Observation on Use of ACTH and Cortisone in Ocular Inflammatory Disease, Am. J. Ophth. **33**:1325 (Sept.) 1950.

3. McLean, J. M.; Gordon, D. M., and Koteen, H.: Clinical Experiences with ACTH and Cortisone in Ocular Diseases, Tr. Am. Acad. Ophth. **56**:565 (May-June) 1951.

4. Mason, H. L.; Hoehn, W. M., and Kendall, E. C.: Chemical Studies of the Suprarenal Cortex: Structures of Compounds C, D, E, F, and G, J. Biol. Chem. **124**:459 (July) 1938.

5. Thorn, G. W.: The Adrenals in Health and Disease, Tr. & Stud. Coll. Physicians Philadelphia **19**:95 (Feb.) 1952.

6. Nelson, D. H.; Reich, H., and Samuels, L. T.: Isolation of Steroid Hormone from the Adrenal-Vein Blood of Dogs, Science **111**:578 (May 26) 1950. Conn, J. W.; Louis, L. H., and Fajans, S. S.: Technical Papers: Probability That Compound F (17-Hydroxycorticos-

costerone (Compound B) and androgenic steroids are also secreted.[5] We are concerned principally with hydrocortisone, and Dougherty [7] has shown that it is the principal corticoid with anti-inflammatory activity at tissue level. Hydrocortisone (17-hydroxycorticosterone) differs from cortisone (11-dehydro-17-hydroxycorticosterone) by having a hydroxyl instead of a ketone group in the carbon-11 position.

Hydrocortisone can be given systemically or locally. Thorn and associates [8] compared the eosinopenic activities of orally administered cortisone and hydrocortisone. On the basis of this response, orally administered hydrocortisone and its acetate were found to be more active than cortisone acetate. The duration of action of orally administered cortisone or hydrocortisone is definitely less than that when the drug is administered intramuscularly. Conn and associates [9] compared the metabolic effects of orally and parenterally administered hydrocortisone and hydrocortisone acetate. Free hydrocortisone when given intramuscularly produced intense metabolic changes. Hydrocortisone acetate showed only a mild effect, but free hydrocortisone and hydrocortisone acetate when given orally produced the same intense changes as those noted with parenterally administered free hydrocortisone.

In systemic therapy, hydrocortisone has the advantage over cortisone in acute cases in which a high level of circulating adrenal cortex hormone is required; also, the maintenance dose of hydrocortisone is less than that of cortisone.[10] Hollander and associates [11] have shown that hydrocortisone is much more effective than cortisone in the local therapy of rheumatoid arthritis. The drug was injected directly into the affected joint or bursa. The suggested explanation for the superior performance of hydrocortisone was that since it is only one-seventh as soluble [11] as cortisone in plasma a sufficient reservoir of the compound might remain in the joint space to give alleviation of the symptoms.

The modus operandi of the adrenal steroids in blocking inflammatory reactions is still unknown. It has been shown by Leopold and associates [1] and by others that their effectiveness when administered locally is not dependent on systemic absorp-

terone) Is the Hormone Produced by the Normal Adrenal Cortex, ibid. **113**:713 (June 22) 1951. Mason, H. L.: Isolation of Adrenal Cortical Hormones from Urine: 17-Hydroxycorticosterone and 17-Hydroxy-11-Dehydrocorticosterone, J. Biol. Chem. **182**:131 (Jan.) 1950. Pincus, G.: Chemistry of Cortisone and Compound F, in Symposium on Cortisone and Compound F, Cincinnati, University of Ohio College of Medicine, May 1, 1952.

7. Dougherty, T. F.: Animal Investigative Studies on Cortisone and Compound F, in Symposium on Cortisone and Compound F, Cincinnati, University of Ohio College of Medicine, May 1, 1952.

8. Thorn, G. W.; Renold, A. E.; Wilson, D. L.; Frawley, T. F.; Jenkins, D.; Garcia-Reyes, J., and Forsham, P. H.: Clinical Studies on the Activity of Orally Administered Cortisone, New England J. Med. **245**:549 (Oct. 11) 1951.

9. Conn, J. W.; Louis, L. H.; Fajans, S. S.; Johnson, B. J.; Barott, G. W.; Hogg, L. W.; Blood, J. P., and Weiss, M.: Metabolic Effects in Man of Orally and Parenterally Administered Compound F (17-Hydroxycorticosterone) and Compound F Acetate, J. Lab. & Clin. Med. **38**:799 (Nov.) 1951.

10. Boland, E. W., and Headley, N. E.: Compound F Used Orally in Patients with Rheumatoid Arthritis, J. A. M. A. **148**:981 (March 22) 1952.

11. Hollander, J. L.; Brown, E. M., Jr.; Jessar, R. A., and Brown, C. Y.: Hydrocortisone and Cortisone Injected into Arthritic Joints: Comparative Effects of and Use of Hydrocortisone as a Local Antiarthritic Agent, J. A. M. A. **147**:1629 (Dec. 22) 1951.

tion. Since hydrocortisone is believed to be the principal steroid with antiinflammatory action at tissue level [7] and since it is absorbed slowly,[11] it might be superior to cortisone for local therapy in ocular disease.

## CLINICAL STUDY

The present study was undertaken to determine whether cortisone and hydrocortisone differed in their action. A small supply of hydrocortisone was made available,[12] and preliminary trials of a few patients showed that it was as effective as cortisone. This confirmed the report of Smith and Steffensen.[13] However, because of its relative scarcity, the drug was subsequently given only to patients who had failed to respond to treatment with cortisone or other therapy. Hydrocortisone was administered locally in drop form in a 1:4 dilution in 1:10,000 benzalkonium (zephiran®) chloride or by a subconjunctival injection of 0.1 cc. of the undiluted product (2.5 mg.).

At the time of preparation of this report, 46 patients have been treated with hydrocortisone. Twenty-eight of them have also been treated with cortisone locally and a few of these with cortisone systemically. With the realization that the cortical steroids do not cure, but merely block the inflammatory action at tissue level, the patients were all subjected to the usual clinical investigative studies. Some of the patients were hospitalized and had received the usual local and sytemic therapy, including administration of cortisone, before hydrocortisone was tried. The others were studied and treated on an ambulatory basis.

Table 1 summarizes our results. The four patients with vernal conjunctivitis had had thorough allergy studies. They had been desensitized to house dust, pollens, etc.; administration of antibiotics for their secondary infection, beta radiation for their conjunctival lesions, and cortisone locally had not relieved their symptoms. Systemic cortisone therapy had given great relief, but it could not be continued indefinitely. One young patient had received cortisone systemically for many months and showed the typical moon face of overtreatment. Hydrocortisone, given in the form of drops four times a day, produced dramatic and continued relief of the symptoms.

Two patients with uveitis and secondary glaucoma received corticotropin, cortisone locally and systemically, and fever therapy without benefit, but responded well to hydrocortisone given by subconjunctival injection and as drops. Two other patients, with uveitis and secondary glaucoma, did not respond to local or systemic administration of cortisone or hydrocortisone. The two patients with keratitis metaherpetica were much more comfortable under treatment with hydrocortisone than when receiving cortisone and the inflammatory reaction was less, but neither drug effected a cure. The lesions were finally cauterized with iodine, and this may have hastened the resolution slightly. Hydrocortisone, however, reduced the discomfort. This antiphlogistic action of hydrocortisone definitely exceeded that of cortisone. When the supply was exhausted and the patients were given cortisone without their knowledge, they frequently thought the eye was worse because they were more uncomfortable.

In most instances patients with anterior uveitis respond to local cortisone therapy. It proved rather difficult to find patients resistant to cortisone in whom hydrocortisone could be tried. However, in two patients with postoperative uveitis and in two others with uveitis the effects of the two drugs could be compared. The

12. Merck & Company, Inc., supplied the hydrocortisone.

13. Smith, R. W., Jr., and Steffensen, E. H.: ACTH and Cortisone in the Treatment of Ocular Disease, New England J. Med. **245**:972 (Dec. 20) 1951; **245**:1007 (Dec. 27) 1951.

TABLE 1.—*Data on Treatment of Ocular Diseases with Cortisone and Hydrocortisone*

| Diagnosis | No. of Cases | Cortico-tropin | Cortisone | | | | | | | Hydrocortisone | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Systemic | Local | | Cyclo-plegia | Other Therapy | Fever | Result | Injection | Drops | Result |
| | | | | Injection | Drops | | | | | | | |
| Vernal conjunctivitis with secondary infection | 4 | .. | + | .. | + | .. | Antibiotics Desensitization Beta-Irrad. | .. | + on Systemic Cortisone | .. | + | + + |
| Uveitis with secondary glaucoma | 1 | + | + | + | + | + | .. | + | — | + | + | + + 3 Mo |
| Uveitis with secondary glaucoma | 3 | .. | .. | + | + | + | .. | + | 1 ± 2 — | .. | + | 1 + + 2 — |
| Uveitis | 3 | .. | .. | + | + | +* | .. | .. | ± | .. | + | + + |
| Episcleritis | 2 | .. | .. | .. | + | + | .. | .. | — | .. | + | + + |
| Phacoanaphylactica | 1 | .. | .. | + | + | +* | .. | .. | ± | .. | + | + + |
| Phacoanaphylactica | 1 | .. | .. | + | + | + | .. | + | ± | .. | + | + + |
| Sympathetic ophthalmia | 2 | + | + | + | + | + | .. | .. | ± | .. | + | + |
| Sympathetic ophthalmia | 1 | + | + | + | + | + | .. | .. | — | + | + | — |
| Keratitis metaherpetica | 2 | .. | .. | + | + | + | Iodine | .. | ± | + | + | ± |
| Keratitis profunda | 1 | .. | .. | + | + | + | .. | .. | ± | + | + | ± |
| Postoperative uveitis | 2 | .. | .. | + | + | +* | .. | .. | — | .. | + | + |
| Rosacea keratitis | 2 | .. | .. | .. | ± | .. | B complex anti-histaminics | .. | ± | .. | + | ± |
| Staphylococcic marginal ulcer | 1 | .. | .. | .. | + | + | Oxytetra-cycline | .. | ± | .. | + | + |
| Blood staining of cornea | 2 | .. | .. | .. | + | .. | .. | .. | — | .. | + | — |
| Anterior uveitis | 10 | .. | .. | .. | .. | + | .. | .. | .. | + | + | + + |
| Allergic conjunctivitis | | | | | | | | | | | | |
| 1 penicillin | 2 | .. | .. | .. | .. | .. | .. | .. | .. | .. | + | + |
| 1 atropine | | | | | | | | | | | | |
| Phlyctenular keratoconjunctivitis | 2 | .. | .. | .. | .. | .. | .. | .. | .. | .. | + | + |
| Lime burn (mild) | 1 | .. | .. | .. | .. | + | .. | .. | .. | + | + | + + |
| Lime burn (severe) | 1 | .. | .. | .. | .. | + | .. | .. | .. | + | + | ± |
| Band keratitis | 1 | .. | .. | .. | .. | .. | .. | .. | .. | .. | + | — |
| Keratitis sicca | 1 | .. | .. | .. | .. | .. | .. | .. | .. | .. | + | — |

* Sensitive to atropine, scopolamine and homatropine.

response to hydrocortisone was definitely superior to that to cortisone. The same held true in a patient with a staphylococcic marginal ulcer.

A total of 18 patients were treated with hydrocortisone alone. In this small series the spectrum of activity of hydrocortisone appeared to be the same as that of cortisone. In some instances the results were dramatic, but equally good results in similar cases have previously been noted with cortisone.

In our clinical studies on this small series we have noted several interesting features. One is that when hydrocortisone is injected subconjunctivally the yellowish-white deposit in the tissue is absorbed much more slowly than is cortisone. In some instances it is visible even after three weeks. This finding may be related to the solubility of the drug, since hydrocortisone is only one-seventh as soluble in plasma as is cortisone.[11] This slow absorption may insure higher tissue concentrations over longer periods of time and reduce the necessity for repeated injections. We have also noted that some patients who did not respond to cortisone when used locally, but who subsequently responded to hydrocortisone, maintained this improvement when cortisone was later substituted for hydrocortisone. Mention has also been made of the greater antiphlogistic action of hydrocortisone. This was especially noted in patients with corneal lesions.

## EXPERIMENTAL STUDY

In an effort to compare the ocular effects of hydrocortisone and cortisone, a series of experimental studies were performed.

*Effect of Hydrocortisone on Epithelial Regeneration.*

Procedure: Standard corneal abrasions were made in both eyes of six normal rabbits. Hydrocortisone was instilled into the right eye in a 1:4 dilution, one drop every hour for the first day, then one drop every three hours for five days. At night 0.1 cc. was injected subconjunctivally.

Result: By the fourth day there was practically no staining of the treated or the control eyes, and by the sixth day there was complete healing of both eyes.

*Effect of Hydrocortisone on Permeability of Normal Eye to Fluorescein.*

Procedure: One drop of hydrocortisone was instilled every five minutes for six drops into the right eye of six normal rabbits. One-half hour after instillation of the last drop, 1 cc. of a 10% solution of fluorescein sodium was injected intravenously.

Result: Slit-lamp examination did not reveal any appreciable difference between the treated and the control eyes in the time that fluorescein appeared in the anterior chamber.

*Effect of Cortisone and Hydrocortisone upon Intraocular Pressure.*

Paracentesis in the normal rabbit eye is followed by a change in pressure, which follows a characteristic curve, the sequence being a primary rise in pressure within 15 to 20 minutes; a fairly rapid drop after a peak is reached, and, within an hour, a secondary rise, which is more gradual and not as marked.

The primary rise in pressure has been explained as due to the dilatation of the capillaries and the formation of plasmoid aqueous. The secondary rise is due to the difficulty of outflow of the secondary aqueous. Leopold and Day [14] have shown this

14. Leopold, I. H., and Day, R.: Influence of Drugs on Restoration of Intraocular Pressure in Normal Eyes After Paracentesis, A. M. A. Arch. Ophth. **45**:233 (Feb.) 1951.

curve to be more pronounced when paracentesis is preceded by instillation of diisopropyl fluorophosphate.

Procedure: Of three groups of five rabbits each, one group served as controls; the second group was given 2.5 mg. of cortisone subconjunctivally in both eyes, and the third, the same amount of hydrocortisone, two hours prior to paracentesis. The three groups were then given 1 drop of diisopropyl fluorophosphate, 0.1%, three times 15 minutes before the paracentesis. The paracentesis was performed with a slanting corneal puncture with a hypodermic needle in order to prevent leakage of aqueous.

Result: Characteristic curves were produced for each group, as shown in the chart (Fig. 1). The averages of the pressures of 10 eyes when plotted indicate that there was no significant change in the eyes receiving cortisone or hydrocortisone as compared with the control eyes.

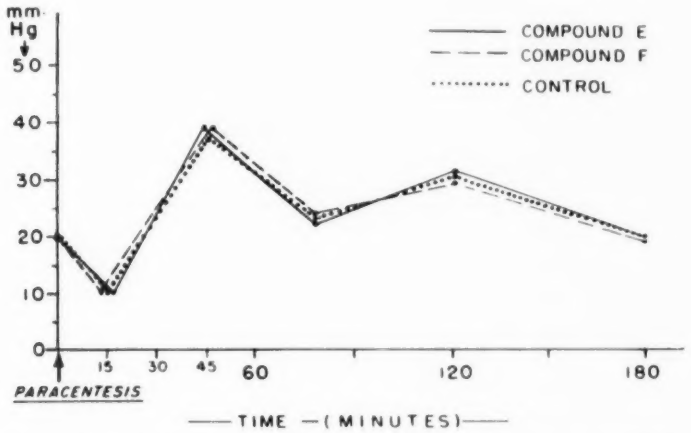


Fig. 1.—Effect of hydrocortisone and cortisone (broken and solid lines respectively) on intraocular pressure of instillation of diisopropyl fluorophosphate and paracentesis. Values for controls are represented by the line of dots.

*Action of Cortisone and Hydrocortisone on the Penetration of an Antibiotic, Streptomycin, into the Anterior Chamber of the Inflamed Eye.*

Increased permeability of the capillary wall is a constant finding in inflammatory lesions, and cortisone has been shown successfully to block the inflammatory and exudative phases of iritis due to hypersensitivity and irritants.[15] The permeability of the capillary wall to fluorescein has been shown to be unaltered in the normal eye and to be decreased in the inflamed human eye by cortisone, administered either locally or parenterally.[16] This reduction in the passage of fluorescein into the anterior chamber of the inflamed eye which has been treated with cortisone may

15. Leopold and others.[1] Woods.[2] Woods, A. C., and Wood, R. M.: Action of ACTH and Cortisone on Experimental Ocular Inflammation, Bull. Johns Hopkins Hosp. **87**:482 (Nov.) 1950. Duke-Elder, S., and Ashton, N.: Action of Cortisone on Tissue Reactions of Inflammation and Repair, with Special Reference to the Eye, Brit. J. Ophth. **35**:695 (Nov.) 1951.

16. Leopold and others.[1] Cook, C., and MacDonald, R. K.: Effect of Cortisone on the Permeability of the Blood-Aqueous Barrier to Fluorescein, Brit. J. Ophth. **35**:730 (Nov.) 1951.

be secondary to a reduction in the tissue reaction or to a direct action of cortisone on the capillary wall. The question is raised whether if cortisone reduces the permeability of the capillary wall of the inflamed eye to fluorescein it might not also reduce the permeability of the capillary wall to antibiotics in the inflamed eye and thus interfere possibly with the maintenance of therapeutic levels within the eye. Systemically administered streptomycin has been shown to pass poorly into the ocular tissues and fluids of the normal eye and to penetrate better in the inflamed eye.[17]

Procedure: Standard lesions consisting of an alkali burn made with a sodium hydroxide pellet on the limbus at the 6-o'clock position and an injection of 500 Escherichia coli organisms into the cornea were made on both eyes of 30 rabbits. The animals were divided into four groups. It was found that the cortisone preservative, 1.5% benzyl alcohol in the undiluted solution, had a definite bactericidal effect, equivalent to 6γ of streptomycin. Therefore, the hydrocortisone and cortisone used were washed in order to eliminate any possible additive bactericidal effect of the benzyl alcohol, which would give a higher streptomycin reading for the treated eye. Streptomycin analyses were done by bioassay.[18]

Results: It can be seen in Table 2 that the groups treated with washed and unwashed cortisone and hydrocortisone, 2.5 and 7.5 mg., respectively, two hours prior to administration of streptomycin, the group receiving 2.5 mg. one-half hour prior to administration of streptomycin, and the group receiving cortisone systemically all showed substantially the same average levels of streptomycin and that the streptomycin levels in the treated eye did not differ from those in the untreated eye.

Conclusions: Neither cortisone nor hydrocortisone, when topically or subconjunctivally administered one-half hour prior to systemic treatment with streptomycin or when given over a period of 2½ hours prior to use of streptomycin, appreciably affect the passage of streptomycin across the blood-aqueous and blood-vitreous barriers in the inflamed eye.

Cortisone and hydrocortisone given systemically in the dose utilized does not affect the penetration of streptomycin from the blood stream into the inflamed eye.

*Effect of Cortisone and Hydrocortisone on Corneal Vascularization Following Injury of the Cornea.*

The use of alloxan as a means of producing a standard vascular lesion has been developed by Ashton, Cook, and Langham.[19] This method produces a minimal, and in most instances a standard, lesion.

Procedure: One group of five rabbits served as controls; the other groups, of four each, were treated with cortisone and hydrocortisone. Each rabbit was given 0.1 cc. (2.5 mg.) subconjunctivally three times a day for six days and then once daily for six days. Treatment was started on the day of intracameral injection of 0.1 cc. of 0.3 M solution of alloxan monohydrate.

All the animals were examined daily. The degree of corneal opacity and the extent of vascularization were noted, and the amount of corneal thickening was estimated. Drawings were made of the appearance of the corneas on the 2d, 7th, and 11th days (Fig. 2).

17. Leopold, I. H., and Nichols, A.: Intraocular Penetration of Streptomycin Following Systemic and Local Administration, Arch. Ophth. **35**:33 (Jan.) 1946.

18. Ann Nichols, of the Harrison Department of Surgical Research of the University of Pennsylvania, aided in these analyses.

19. Ashton, N.; Cook, C., and Langham, M.: Effect of Cortisone on Vascularization and Opacification of the Cornea Induced by Alloxan, Brit. J. Ophth. **35**:718 (Nov.) 1951.

TABLE 2.—*Effect of Cortisone on Penetration of Antibiotic into Inflamed Eye**

Streptomycin Levels, Micrograms

| With Benzyl Alcohol | | | | Benzyl Alcohol Removed | | | |
|---|---|---|---|---|---|---|---|
| Aqueous | | Vitreous | | Aqueous | | Vitreous | |
| O. D. | O. S. | O. D. | O. S. | O. D. | O. S. | O. D. | O. S. |
| **Standard Lesions O. U.: 2.5 Mg. Cortisone O. D. Subconjunctivally 2 Hr. and 7.5 Mg. Cortisone ½ Hr. Prior to Streptomycin, 20,000 U./Kg./I. M.** | | | | | | | |
| 6 | 10 | 1.4 | 4 | >1 | >1 | 2 | 2 |
| >1 | 3 | 3.5 | 1.5 | 7 | 5.5 | >1 | 3 |
| 4 | 8 | 4.5 | 3 | 8 | 5.5 | 3 | 3 |
| 7 | 10 | 2.5 | 0 | 4 | 7 | >1 | 1.5 |
| 2.5 | 6 | 1.5 | 1.5 | 5.5 | 4.5 | 0 | 2.5 |
| 4.1 | 7.1 | 2.8 | | 4.7 | 4.5 | 1.6 | 2.4 |
| **Standard Lesions O. U.: 2.5 Mg. Hydrocortisone 2 Hr. and 7.5 Mg. Hydrocortisone (Compound F) O. D. Subconjunctivally ½ Hr. Prior to Streptomycin, 20,000 U./Kg./I. M.** | | | | | | | |
| 4 | 4 | 0 | 0 | >1 | 4.5 | 2 | 0 |
| 2.5 | 2 | 2 | 0 | 5.5 | 7 | 0 | 1.5 |
| 1.5 | 3 | 1.5 | 1.5 | 4 | 3 | 3.5 | 0 |
| 6.0 | 4 | ... | ... | 10 | 7 | >1 | 2 |
| 3 | 3 | ... | ... | 4.5 | 5.5 | 2 | 1.5 |
| 3.5 | 3.5 | 1.1 | 0.5 | 4.8 | 5.4 | 1.9 | 1 |
| **Standard Lesions O. U.: 2.5 Mg. Cortisone O. D. ½ Hr. Prior to Streptomycin, 20,000 U./Kg./I. M.** | | | | | | | |
| 3 | 3 | 0 | >1 | | | | |
| 3 | 3 | 1 | 1.5 | | | | |
| 4 | 4 | 0 | 0 | | | | |
| 10 | 10 | 1.5 | ? | | | | |
| 4 | 4 | 2 | 0 | | | | |
| 4.8 | 4.8 | 0.9 | 0.4 | | | | |
| **Standard Lesions O. U.: 2.5 Mg. Hydrocortisone ½ Hr. Prior to Streptomycin, 20,000 U./Kg./I. M.** | | | | | | | |
| 4.5 | 4 | 2 | 1.5 | | | | |
| 6 | 4 | <1 | <1 | | | | |
| 4 | 4.5 | 0 | 0 | | | | |
| 2.5 | 4.5 | 0 | 0 | | | | |
| ... | ... | ... | ... | | | | |
| 4.5 | 4.2 | 0.6 | 0.5 | | | | |
| **Standard Lesions O. U.: 2.5 Mg. Cortisone I. M. t. i. d. for Two Days Prior to Streptomycin, 20,000 U./Kg./I. M.** | | | | | | | |
| 4† | 6† | 1† | 1† | | | | |

**Bactericidal Levels (Micrograms) of Compounds E and F Given Alone**

| With Benzyl Alcohol | | Benzyl Alcohol Removed | |
|---|---|---|---|
| Compound E | | Compound E | |
| Undiluted | 6 | Undiluted | <1 |
| 1/10 dilution | 1 | 1/10 dilution | <1 |
| 1/100 dilution | 1.3 | 1/100 dilution | <1 |
| 1/1000 dilution | 1.5 | 1/1000 dilution | <1 |
| Compound F | | Compound F | |
| Undiluted | 6 | Undiluted | <1 |
| 1/10 dilution | 1 | 1/10 dilution | <1 |
| 1/100 dilution | >1 | 1/100 dilution | <1 |
| 1/1000 dilution | >1.2 | 1/1000 dilution | <1 |

* The data in this Table demonstrate that hydrocortisone and cortisone given locally possess a bactericidal effect which is due to the benzyl alcohol content. The values in each table are expressed in micrograms of streptomycin, determined by bioassay. It is evident that neither hydrocortisone nor cortisone influences the intraocular penetration of systemically administered streptomycin.

† Averages for four eyes.

Results: On the second day after the injection all the corneas displayed opaqueness, ranging from slight clouding of the stroma to dense opacification obscuring the details of the anterior chamber. In several days the opacity was restricted to one sector of the cornea. By the 11th day, of the eight eyes treated with hydro-

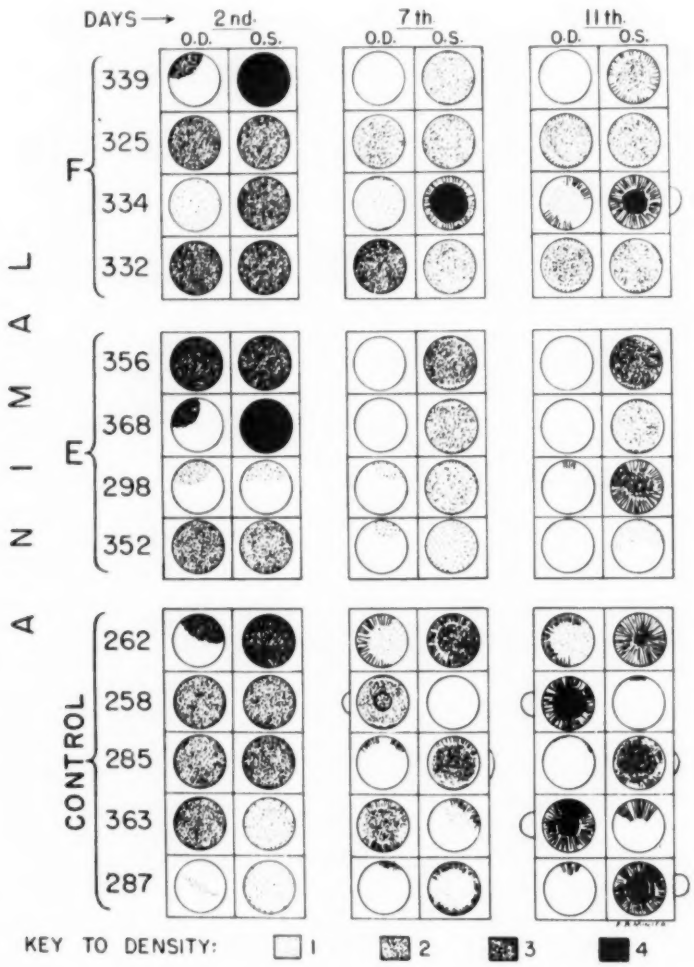


Fig. 2.—Corneal vascularization following intracameral injection of a 0.31 M solution of alloxan monohydrate.

cortisone there were a slight decrease in the opacity in six, complete clearing in one, and no change in one.

In the cortisone group there were complete clearing in four eyes, a slight decrease in the opacity in two, a marked increase in one eye, and no change in one eye. In the control group there were clearing in three eyes and moderate to marked increase in the opaqueness in seven eyes.

Extent and Density of Vascularization: The presence of vessels was noted as early as the fifth day in a few eyes. In the group treated with hydrocortisone three eyes showed neovascularization from 0.1 to 1 mm. in length by the seventh day. By the 11th day all the eyes but one showed vessels varying in length from 0.5 to 2.5 mm. One eye was completely girdled with vessels.

Of the eyes treated with cortisone, three displayed the ingrowth of vessels on the seventh day in the same manner as the eyes treated with hydrocortisone. On the 11th day five eyes showed neovascularization, while three were clear.

On the seventh day all but one of the control group showed neovascularization of 0.5 to 2 mm. in length. On the 11th day all the eyes showed some degree of vascularization, ranging from very faint localized groups of vessels to complete girdling of the limbus and dense vessels 0.5 to 4 mm. in length.

Swelling of the Cornea: There was marked swelling of the corneas with diffuse clouding of the stroma; as far as could be determined visually, the thickness was twice that of the normal cornea.

By the seventh day massive swelling developed in several eyes to such a degree that the cornea resembled the curvature of keratoconus. This was more prominent in the control groups. By the 11th day this phenomenon was noted in five eyes of the control group.

Conclusions: The application of cortisone and hydrocortisone resulted in noticeable and significant depression of density, number, and length of vessel ingrowth in the corneas of animals receiving intracameral injections of alloxan. The suppression of neovascularization was somewhat more marked in the cortisone-treated group than in the hydrocortisone-treated group. The accompanying edema of the cornea was also noticeably less in the treated animals, but there was no significant difference between the two treated groups.

*Effect of Cortisone and Hydrocortisone on the Healing of Corneal Wounds.*

There is much experimental and clinical evidence to indicate that cortisone inhibits the cellular infiltrate and fibroblastic activity associated with inflammation and the formation of granulation tissue in the eye and in the body generally.[20]

Procedure: In this study standard corneal lacerations were produced in three groups of six animals each. One group received 2.5 mg. of cortisone subconjunctivally three times a day for six days and the same amount once a day until the 10th day. Hydrocortisone was given in the same manner to another group, while the third group served as controls. One animal from each group was killed and its eyes were sectioned on the 1st, 2d, 5th, 6th, 7th, and 10th days, respectively. The corneal laceration was made centrally through the entire thickness of the cornea for a distance of about 5 mm.

Results: The series of six slides covering the 10 days was not strictly progressive owing to the individual reactions of each animal, but they did show a general gradation in the progress of the healing (Fig. 3).

In the control group on the first day there were a much larger amount of fibrinpus exudate and a much denser cellular infiltration, especially at the lips of the wound. The invasion of fibroblasts was evident by the fifth day, and by the seventh

20. Leopold and others.[1] Newell, F. W., and Dixon, J. M.: Cortisone and Union of Corneal Grafts, Am. J. Ophth. **34**:977 (July) 1951. Ragan, C. A., and others: Effect of Cortisone on Production of Granulation Tissue in the Rabbit, Proc. Soc. Exper. Biol. & Med. **72**:718 (Dec.) 1949.

day there was a beginning lamellar arrangement. This was very definite by the 10th day. The laceration was practically healed by the seventh day, with the anterior and posterior surfaces of the cornea covered by the epithelium and endothelium.

In the groups treated with cortisone and hydrocortisone there was marked suppression of the fibroblastic growth throughout the time of the experiment. By the 10th day there were only rudimentary efforts at invasion of the fibrinous coagulum and early symmetrical arrangement of the fibroblasts. The epithelial growth was almost as much as in the control group, but the arrangement of the cells was haphazard and in some places followed the lips of the wound down almost to within the anterior chamber. Endothelial regeneration appeared to be retarded

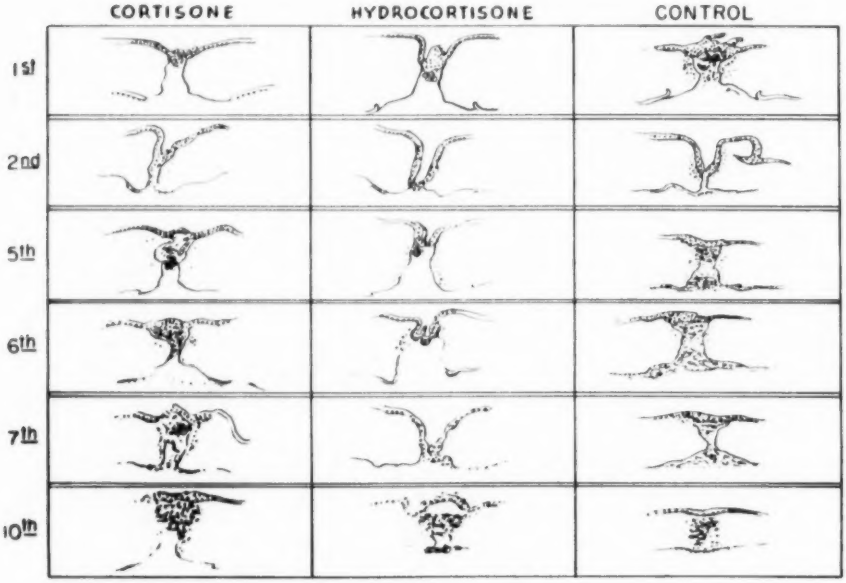


Fig. 3.—Influence on wound healing of cortisone and hydrocortisone.

It is apparent that cortisone and hydrocortisone have a strong inhibitory effect on the formation of fibrinous exudate, the ingrowth of fibroblasts, and the cellular infiltrate usually found in the healing of corneal wounds. The effect seems to be the same with the two compounds.

## SUMMARY

A total of 46 patients were treated with hydrocortisone either in the form of drops or by subconjunctival injection. Twenty-eight had previously been treated with cortisone locally or systemically. Hydrocortisone was found to give significantly better results than cortisone in 18 of these patients. This was especially so in four patients with vernal conjunctivitis, in whom the response was dramatic. In no instance was cortisone found to be effective when hydrocortisone was ineffective. The spectrums of activity of the two compounds seem to be about the same, though hydrocortisone would appear to be more potent. The subconjunctival deposit

of hydrocortisone remains in the tissues much longer than that with cortisone. The antiphlogistic action of hydrocortisone appears to be greater than that of cortisone

Cortisone (Compound E) and hydrocortisone (Compound F) were compared in equal doses for their effect on the permeability of the blood-aqueous barrier to fluorescein and streptomycin in the normal and in the inflamed eye. Their effect on corneal vascularization induced by intracameral injection of alloxan and their role in wound healing were also determined. The influence of these compounds on the vasodilatation induced by paracentesis and by an anticholinesterase agent, diisopropyl fluorophosphate, was studied.

Both compounds failed to influence the permeability of the blood-aqueous barrier of the normal eye to fluorescein. Both compounds failed significantly to reduce the permeability of the inflamed eye to streptomycin. The two hormonal substances failed to influence the vasodilatation and intraocular pressure curve induced by paracentesis and diisopropyl fluorophosphate. Paracentesis probably produces its vascular and intraocular pressure effects by liberation of histamine, as well as reducing the supporting pressure on the intraocular vessels, and diisopropyl fluorophosphate, its effect by permitting the accumulation of acetylcholine. Since neither hormonal substance blocked these effects, it appears that these compounds have neither an antihistaminic nor an anticholinergic action.

Both compounds inhibited corneal vascularization. Cortisone was a trifle more effective than hydrocortisone in this regard. Both compounds inhibited fibrous tissue proliferation in corneal wounds equally. The experimental methods employed failed to uncover any significant difference in action of these two compounds except for their slight difference in corneal vascularization.

## ABSTRACT OF DISCUSSION

Dr. Frank W. Newell, Chicago: Dr. McDonald and his associates, in their usual competent manner, have presented a comprehensive exposition of their clinical and experimental observations on the use of hydrocortisone. Particularly important is their clinical evidence that hydrocortisone is effective in some patients in whom cortisone has not been effective and that every patient who responds to cortisone responds also to hydrocortisone. My experience with hydrocortisone is more limited than that the authors have reported. My initial impression is that hydrocortisone and cortisone cause very nearly identical responses in most inflammatory conditions. Hydrocortisone appears to be somewhat superior to cortisone for the subjective relief of symptoms. Cortisone, however, frequently causes a prompter objective improvement, particularly in inflammation of the anterior uvea.

When a drug has proved itself as useful as cortisone in ocular disease, it is difficult to prove that a subsequently discovered compound is superior. The problem is further complicated with these steroids by their marked difference in solubility and their widespread cellular and systemic effects. Thus, the apparent superiority of cortisone, hydrocortisone acetate, or free hydrocortisone in a particular condition may be related entirely to its solubility or lack of solubility rather than to any superiority in its physiologic activity. Perhaps for local ocular use a mixture of these steroids will give us all their advantages.

The experimental studies of McDonald and his associates do not indicate any superiority of hydrocortisone over cortisone. Our studies have been similar. In one group of rabbits the eyes were sensitized by the intravitreal injection of horse serum (0.10 cc.). Fourteen days later different groups were given intravenous injections of 5 mg. per kilogram of cortisone, hydrocortisone acetate, or free hydrocortisone. Immediately thereafter 1.0 cc. of horse serum was injected intravenously.

Subsequent ocular inflammation was evaluated daily thereafter. None of the compounds tested appeared to have any effect upon the anaphylactic uveitis.

In other studies, cortisone or hydrocortisone was applied topically (five times at five-minute intervals) to the right eye of albino rabbits, and then diisopropyl fluorophosphate (0.10%) was instilled in each eye. In other rabbits, cortisone was instilled in one eye and hydrocortisone in the other, and then diisopropyl fluorophosphate was instilled. One hour later intracardiac injection of India ink was made, and, after death of the animals, the eyes were enucleated. After formaldehyde fixation the ciliary body and iris were excised and studied. Generally the steroids appeared to suppress the inflammatory response caused by the diisopropyl fluorophosphate, but no difference between hydrocortisone and cortisone could be noted.

Dr. Irving H. Leopold, Philadelphia: I want to thank Dr. Newell for his carefully considered contribution. He has presented a considerable amount of additional data concerning hydrocortisone.

Dr. Newell stressed that some of the differences in these compounds may be due to the differences in solubility, as had been noted previously by Hollander and his associates, in their effort to explain the greater beneficial effect of hydrocortisone than of cortisone when injected locally into arthritic joints.

Eyes with glaucoma and narrow angles which are treated with diisopropyl fluorophosphate occasionally show a rise in intraocular tension. Dr. Newell's observations suggest a benefit from hydrocortisone in the control of this rise in pressure following the instillation of diisopropyl fluorophosphate in some eyes.

This rise in pressure, as was shown by von Sallmann and Haas and others, is probably due to the increased dilatation of the small vessels, particularly at the base of the iris and in the ciliary body. This dilatation allows engorgement of those structures, crowding the angle and allowing a pouring into the eye of plasmoid material, which embarrasses the angle further and, perhaps, causes a rise in intraocular pressure.

Thus, if this vasodilatation can be blocked by the use of cortisone or hydrocortisone following the instillation of diisopropyl fluorophosphate, they might prevent this rise in intraocular pressure.

Unfortunately, the attempts to show this in another way, by means of paracentesis plus instillation of diisopropyl fluorophosphate, and control of the vasodilatation by the use of cortisone and hydrocortisone, as shown by Dr. McDonald and his co-workers, did not confirm this observation.

A few years ago Dr. von Sallmann and his associates showed that diisopropyl fluorophosphate used in 0.2% concentration would cause a rise in intraocular pressure in rabbit eyes, and that this could be overcome by the use of a vasoconstrictor, such as phenylephrine, but that it could not be overcome by adrenocortical extracts that they had available at that time.

# TREATMENT OF CHEMICAL BURNS OF THE EYE

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THE VAST amount of literature on chemical burns of the eye has clearly outlined certain fundamental concepts of the altered physiology present in such injuries, but the application of this information is yet difficult to attain. Our knowledge of the basic mechanisms involved in ocular burns was considerably advanced during the war years through the combined efforts of research workers in this country and abroad. The most noteworthy result of their efforts was the finding of a suitable specific treatment for eyes burned with lewisite ($\beta$-chlorovinyl-2-chloroarsine) by employing dimercaprol, commonly known as BAL (British anti-lewisite). After the fundamental investigations of the Oxford group that led to the use of dimercaprol for lewisite lesions of the skin, Mann [1] and other British investigators were the first to evaluate dimercaprol therapy for ocular lesions.

More recently, calsulfhydryl (hydrosulfosol® [2]) has received attention from ophthalmologists, following a report by Kuhn.[3] This investigator summarized her findings over a period of three years in more than 300 cases of major chemical and thermal burns of the eye which had been treated with ophthalmic calsulfhydryl. The conclusions were that with its use pain was controlled, healing was more rapid, visual restoration was accelerated, permanent disability was reduced, and there were fewer indications for conjunctival flaps. The usefulness of this substance was based on its apparent value as a specific therapeutic agent for eye burns because of its chemical composition and a reputed ability to stimulate healing functions related to biochemical aspects of this particular organ. Calsulfhydryl, Kuhn indicated, has also been a valuable adjunct in the treatment of ocular injuries caused by anhydrides and detergents. Cruthirds,[4] Mullen,[5] and Spaeth [6] expressed approval of this compound for the treatment of ocular burns. It has been reported that numerous

Paper presented at the annual clinical congress of the American College of Surgeons, New York, Sept. 25, 1952.

1. Mann, I.: Report on the Effect of Liquid D T H, England W 14215, W A-352-4, 1942 (Restricted information).

2. Hydrosulphosol® is the E. C. Lientz and Co. name for their brand of sulfhydryl.

3. Kuhn, H. S.: Use of Hydrosulphosol® (Sulphydryl) in the Treatment of Clinical and/or Thermal Burns of the Eyes, Tr. Am. Acad. Ophth. **53**:157, 1948.

4. Cruthirds, A. E.: Importance of Sulfhydryl in Treatment of Corneal and X-Ray Burns, Am. J. Surg. **72**:500-509, 1946.

5. Mullen, C.: Decisions in Eye Injuries, J. Aviation Med. **21**:61, 1950.

6. Spaeth, E. B.: Industrial Ophthalmology, Tr. Am. Acad. Ophth. **55**:725-732, 1950.

ophthalmologists in the United States have been impressed by the efficacy of this material in clinical treatment.

However, in contrast to reports on the extensive work done on dimercaprol, no reference to chemical burns of the eye in laboratory animals treated with calsulfhydryl could be found in the literature. It seemed advisable, therefore, to run a series of controlled experiments on the eyes of a suitable laboratory animal to determine whether the results agreed with the clinical experience of those who had reported on calsulfhydryl.

Chemical burns of the cornea differ in their rate of onset, symptoms, depth of involvement in the cornea and conjunctiva, and eventual prognosis. Certain factors are generally recognized as prominent in determining the nature and extent of injury, such as (1) the amount and duration of exposure, (2) the reactivity of the noxious substance with tissue components, and (3) the physical characteristics which determine penetration of the chemical through cell membranes and its direct effect on these membranes (Grant [7]).

In my experiments for the determination of the efficiency of calsulfhydryl in the treatment of various chemical burns, the following chemicals in varying strengths were used: hydrochloric acid, sodium hydroxide, maleic anhydride, acetic acid, iodoacetate, sulfuric acid, creosol, lactic acid, and calcium oxide (lime). My aim was to produce a standard, reproducible lesion of moderate severity; therefore considerable attention was given to the strength of the material and the duration of the exposure. It can be understood at once that a maximal lesion is unsuited for antidote evaluation.

A total of 157 rabbit eyes were tested with chemical agents. Thirty-five eyes were used purely for the production of standard lesions and did not enter into the final results of the tested eyes. Fifty-three pairs of rabbit eyes were selected for the experiment dealing with calsulfhydryl in treatment of the chemically injured eyes. The few remaining eyes were used in interesting corroborating studies.

The results showed that the calsulfhydryl-treated eye was neither better nor worse than the control eye, in which no treatment was used. Statistical analysis of these figures by the chi-square technique indicated that the probability that the calsulfhydryl-treated eye differed from the control eye was less than 1%. This evidence supported the hypothesis that the choice of calsulfhydryl was a matter of indifference.

Information regarding the production of various types of standard lesions, the problems introduced by secondary infection, and the methods of grading the severity of the lesions are too detailed for this paper but have been included in a previous report (Harley [8]).

In the case of 0.001 M iodoacetate solution, 0.02 cc. of which was injected intracorneally, the results differed from the usual pattern. The calsulfhydryl-treated eye showed some improvement over the control eye in three pairs. This observation was in accord with the known enzyme-inhibiting properties of iodoacetate. However, maleic anhydride, which belongs to the same selective inhibiting

7. Grant, W. M.: Chemical Burns of the Eye, Tr. Sect. Ophth., A. M. A., 1949, p. 27.

8. Harley, R. D.: Experimental Study on the Evaluation of Hydrosulphosol in Treatment of Ocular Injuries Due to Chemical Burns, Tr. Am. Ophth. Soc. **56**:557, 1951.

class of agents, showed no difference in the response to calsulfhydryl medication, which is theoretically capable of delivering an excess of the sulfhydryl ions to the tissue.

The basic aim of this study was the evaluation of sulfhydryl as contained in calsulfhydryl in the treatment of chemical burns of the rabbit eye. While this investigation was not intended as a complete critical estimation of the use of sulfhydryl in chemical burns, yet, as an introduction to controlled animal experiments for the study of this compound, certain interesting observations and facts emerged.

The results of these experiments were not all surprising in light of the comprehensive work on acid and alkali burns, the specific-protein denaturants, and the enzyme-inhibiting compounds. In the case of acid burns, increased hydrogen ion concentration of the tissue appears to cause primarily denaturation of proteins. The corneal epithelium is usually conspicuously altered in appearance, presumably because of precipitation of its proteins, and does not undergo dissolution, as in the presence of alkalis.[9] Penetration of the cornea by alkalis is rapid, possibly as a consequence of saponification and destruction of the fatty epithelial barrier.[10] Characteristically, the corneal mucoid is denatured, released, or partially removed from its association with collagen, the principal structural component.

Four pairs of eyes were burned with 1 N HCl by the splash-air jet technique in an effort to determine the effectiveness of calsulfhydryl in acid burns. The paired eyes were well in four or five days, and no difference was detected in the rate of healing for the control or the dimercaprol-treated eyes. Since sulfhydryl is the active principle in both calsulfhydryl and dimercaprol, it is not surprising that the latter was no more successful in the treatment of ordinary acid burns than was calsulfhydryl. The necessity for rapid treatment by the specific antidote has been emphasized by Mann, Pirie, and Pullinger [11] in the use of dimercaprol for lewisite burns. Application of dimercaprol in a 10% solution within five minutes after contamination of the eye with lewisite gave excellent results. For a 20% solution, to still obtain good results, the time can be extended to not more than 15 minutes after contamination. When the time was extended beyond 30 minutes, the eyes were lost despite the energetic use of dimercaprol. It follows that there is a direct relation between the time of application for this specific antidote and the final visual results.

In contrast to the acids and alkalis, certain other compounds react with or become attached to specific groups in the tissue proteins and alter their biological properties. In certain instances the denaturation of certain structural or enzymatic constituents of the cornea can produce specific types of toxic responses. Specific protein denaturants actually combine chemically with the reactive groups characteristic of proteins, such as the sulfhydryl, amino, carboxyl, and hydroxyl radicals (Grant [7]). Some of the known specific-protein denaturants are 2-chloroethyl-sulfur

9. Friedenwald, J. S.; Hughes, W. F., Jr., and Herrmann, H.: Acid Burns of the Eye, Arch. Ophth. **35**:98-108, 1946.

10. Hughes, W. F., Jr.: Alkali Burns of the Eye: Review of Literature and Summary of Present Knowledge, Arch. Ophth. **35**:423-449, 1946.

11. Mann, I.; Pirie, A., and Pullinger, B. D.: Experimental and Clinical Study of the Reaction of Anterior Segment of the Eye to Chemical Injury, with Special Reference to Chemical Warfare Agents, Brit. J. Ophth., Monograph. Supp. 13, 1948.

and nitrogen compounds, methylating agents, arsenicals, certain activated halogen compounds, aldehydes, and lacrimators, such as iodoacetate.

Mackworth [12] has shown that lacrimators, such as ethyl iodoacetate and bromoacetophenone, inhibit all the enzymes which are generally accepted as thiol enzymes, the inhibition being progressive and irreversible in all cases. The enzymes can be protected against the inhibition by reduced glutathione or cysteine. A considerable excess of the simple thiols is required for complete protection. The results obtained on intracorneal injection of iodoacetate in our cases agree with this concept of enzymatic inhibition.

McLaughlin [13] reported on a clinical study of calsulfhydryl in chemical burns in which a series of 52 subjects were observed. Twenty-six patients were treated with calsulfhydryl, and 26 received his unmodified "denuding technique." Each patient treated with calsulfhydryl was paired with a similar patient treated without this compound. The chemicals included in this unselected group of patients were diethyl (ethyl) sulfate, aluminum chloride, carbon disulfide, concentrated acetic acid, phosphorus oxychloride, dibutyl ether, aluminum phosphate, dibutyl tin, sodium sulfide, isopropyl sulfate, vinyl chloride (chloroethylene), acetic anhydride, ethylhexanol (2-ethylhexane-1,3-diol), 50% sodium hydroxide, calcium oxide (lime), maleic anhydride, battery (sulfuric) acid, and, in seven cases an unknown compound. The quantity of the chemical and the time elapsed before treatment was begun could not be controlled.

McLaughlin concluded that calsulfhydryl was only another therapeutic agent for chemical burns of the eye. Its use apparently was not superior to the denuding technique and was actually of questionable value. When it is used for the glutathione effect, antibiotics should be administered. Pain was noted in each instance after the application of calsulfhydryl, and it was found necessary to use anesthetic agents topically in conjunction with this compound or without it.

McLaughlin [14] had previously reported, in 1946, on a study of 500 consecutive cases of chemical burns of the human cornea. Denudation of the corneal epithelium was given as the method of choice in his experience with 103 chemical agents. Immediate irrigation with copious quantities of water was the most important single therapeutic objective. No attempt at neutralization was recommended. The success of this treatment is exemplified by the report that in 91.2% of the cases healing occurred in 48 hours without loss of vision.

## COMMENT

In an attempt to formulate basic concepts in the treatment of ocular burns, one is forced to accept the fact that at present there appears to be no known antidote for all types. The use of dimercaprol in lewisite burns of the eye is specific and illustrates the reversal of an enzyme-inhibiting agent. The most complicated and special forms of treatment have no significant advantage over ordinary care provided that

12. Mackworth, J. F.: Inhibition of Thiol Enzymes by Lachrymators, Biochem. J. **42**:82-90, 1948.

13. McLaughlin, R. S.: Hydrosulphosol as a Treatment of Chemical Burns of the Eyes, Am. J. Ophth. **35**:21, 1952.

14. McLaughlin, R. S.: Chemical Burns of the Human Cornea, Am. J. Ophth. **29**:1355, 1946.

it includes early and thorough irrigation of the eye following contamination by the chemical. In the case of burns with lime and other materials not readily soluble, it may be necessary to remove the particles clinging to the conjunctival surface. Neutralizing solutions have not justified their usefulness.

In the alkali burns, which cause destruction through dissolution of the corneal epithelium and later disintegration of the stroma, early removal of the entire corneal epithelium seems to offer certain advantages, since the products of dissolution are removed from further activity. All patients with ocular burns should be carefully questioned as to the identity of the chemical involved, the concentration, the quantity, and the circumstances of exposure. This information is of considerable aid in determining the course of treatment and the prognosis for restoration of vision.

Chemotherapy or the use of antibiotics which will not interfere with the reparative process is fundamental. All severe burns of the cornea require atropine for the iritis which is nearly always present. In the early stages, denuded surfaces can be prevented from forming adhesions by the frequent and gentle use of a smooth glass rod, aided by a lubricant. Local anesthetic agents should be used as infrequently as possible, owing to their known retarding effect on epithelial regeneration. The use of dressings for one or both eyes, together with general sedation, adds measurably to the comfort of the patient. Paracentesis of the anterior chamber is indicated for ammonia burns and other highly soluble agents to help preserve the functional integrity of the deeper structures. Cortisone used locally or systemically appears to be a valuable substance for inhibiting fibroblastic proliferation and consequently minimzes the final corneal scarring resulting from chemical keratitis (Leopold and Maylath [15]). Corneal vascularization, which is particularly troublesome after severe alkali burns, is likewise inhibited by cortisone (Jones and Meyer [16]).

In special cases of burns early or late mucous-membrane grafting and the repair in final stages by keratectomy or keratoplasty may be indicated, and the question of their usefulness must be resolved by the experience of the surgeon.

## SUMMARY AND CONCLUSIONS

The use of sulfhydryl as found in calsulfhydryl (hydrosulphosol®) in the treatment of ocular burns was studied in a series of controlled experiments with laboratory animals.

A total of 157 rabbit eyes were tested with various chemical agents, including strong acids, strong alkalis, anhydrides, and specific agents designed for enzyme inhibition.

For 53 pairs of rabbit eyes in which corneal lesions were produced with various chemicals, results showed that the calsulfhydryl-treated eye was neither better nor worse than the controlled, untreated eye. With only one chemical, iodoacetate, did calsulfhydryl, in three paired experiments, give consistently better results than those in the controlled eye.

The observation on iodoacetate was in accord with its known enzyme-inhibiting properties and specific-protein-denaturant qualities.

15. Leopold, I. H., and Maylath, F. R.: Intraocular Penetration of Cortisone and Its Effectiveness Against Experimental Corneal Burns, Am. J. Ophth. **35**:1125, 1952.

16. Jones, I. S., and Meyer, K.: Inhibition of Vascularization of Rabbit Cornea by Local Application of Cortisone, Proc. Soc. Exper. Biol. & Med. **74**:102, 1950.

The principal physiopathological effects in and differences between acid and alkali burns are mentioned. The result of the use of sulfhydryl in these lesions followed the expected pattern, that is, its use proved to be a matter of indifference. It would seem logical that the chief sphere of activity for sulfhydryl is in lesions produced by specific enzyme-inhibiting agents which combine chemically with the SH radical.

Caution should be expressed in any attempt to convert results in animal experiments to the clinical evaluations in human subjects. Studies along the line of specific chemical lesions should be considered for further evaluation of this compound.

Present-day concepts of the treatment of ocular burns are outlined and modified in the light of my experience. The technique of "denudation of the cornea" advocated by McLaughlin has certain advantages, especially in alkali burns. Cortisone appears to be of definite value in inhibiting fibroblastic proliferation and corneal vascularization.

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# MIOTIC THERAPY OF CHRONIC GLAUCOMA—CHANGING TRENDS

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THERE are exciting developments in glaucoma research, but the medical treatment of noninflammatory types of chronic glaucoma continues to be primarily with drugs which induce miosis in the normal eye. In recent years, much has been learned about these drugs; a better understanding of the pathogenesis of chronic glaucoma has been reached, and there have been improvements in diagnosis and evaluation of treatment. As a result, miotic therapy no longer is purely symptomatic, with the dosage determined on a trial-and-error basis. It is the purpose of the present report to review some recent developments, particularly as they apply to the treatment of chronic glaucoma.

The hypotensive effect of these drugs on glaucomatous eyes cannot be merely a matter of contraction of the intraocular muscles, because alterations in ocular tension occur which cannot be explained on such a simple mechanical basis; however, the mechanism, intensity, and duration of action of these drugs on the intraocular muscles largely determine their clinical applicability.

Drugs may produce miosis either by relaxation of the iris dilator fibers or by contraction of the iris sphincter (Chart 1). A number of drugs effectively stimulate contraction of the iris sphincter. Commonly used stimulatory miotics are pilocarpine, physostigmine, carbachol U. S. P. (carcholin®), and diisopropyl fluorophosphate. As yet, no drugs have been developed which consistently relax the iris dilator fibers when topically administered; however, there is a group of drugs which induce this type of miosis when administered systemically. N,n-dibenzyl-β-chloroethylamine hydrochloride (dibenamine®) is the best known of this new class of drugs. It blocks the stimulatory effects of epinephrine and therefore is spoken of as an adrenergic-blocking agent. When administered intravenously, dibenamine® may effect a dramatic drop in ocular tension.[1] This hypotensive action cannot be correlated with either the miosis or the variations in systemic arterial pressure. There is experimental evidence that it is due to decreased formation of fluid by the ciliary body.[2]

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Compilation of data on glaucoma therapy was made possible by financial support from the Kellogg Foundation.

1. Christensen, L., and Swan, K. C.: Adrenergic Blocking Agents in the Treatment of Glaucoma, Tr. Am. Acad. Ophth. **53**:489-498 (May-June) 1949.

2. Harris, J. E., to be published.

Dibenamine® has little effect on the ocular tension of the normal eye, but dramatic decreases in ocular tension occur in some cases of acute glaucoma (Chart 2). Unfortunately, the hypotensive action of dibenamine® cannot be maintained for more than a few days, and it has pronounced systemic effects, notably

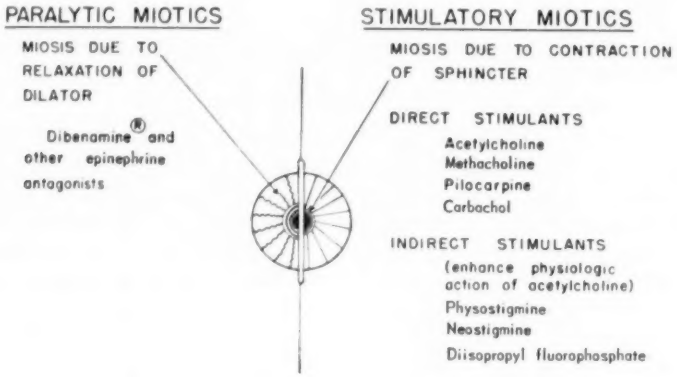


Chart 1.—Action of paralytic and stimulatory miotics.

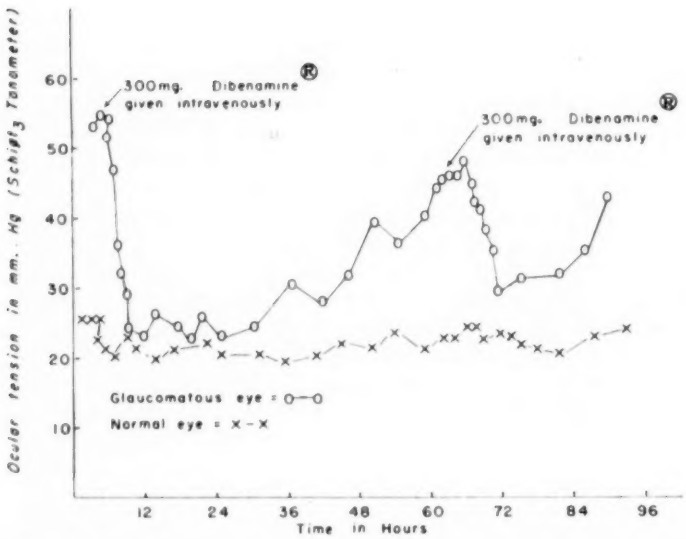


Chart 2.—Influence of intravenous injections of dibenamine® on ocular tension of the glaucomatous left eye and the normal right eye.

orthostatic hypotension. Its clinical use is limited, therefore, to the emergency control of acute glaucoma in hospitalized patients. In this group it has an important place, because it is often effective when other drugs fail. Perhaps the greatest significance of dibenamine® lies in the fact that its use demonstrates the feasibility

of reducing elevated ocular tension by diminishing aqueous formation. New compounds of this class might be developed which would be effective when applied locally. There is evidence, also, that ocular tension might be reduced by compounds which interfere with the enzymatic processes concerned with aqueous formation. These possibilities seem the most hopeful of the several new avenues of approach to the medical treatment of glaucoma.

All topically effective miotics act by stimulating contraction of the iris sphincter and the muscles of accommodation. These muscles are innervated by the parasympathetic nervous system via the third cranial nerve. Stimulation of this nerve is associated with release of acetylcholine at the nerve endings. Acetylcholine is constantly formed in the iris and ciliary body, because the pupil and the mechanisms of accommodation are seldom inactive during the waking hours. Acetylcholine does not have a cumulative effect because its action is terminated by a tissue enzyme, cholinesterase. Any drug which inhibits or blocks the action of this esterase permits physiologically produced acetylcholine to accumulate. Its action is thereby prolonged and enhanced. There are, then, two possible mechanisms by which drugs may stimulate the iris sphincter and the muscles of accommodation. They may stimulate the muscle cells directly. This mode of action is characteristic of acetylcholine, carbachol, pilocarpine, and methacholine (mecholyl®). All are spoken of as cholinergic drugs. Other drugs may induce miosis and contraction of the muscles of accommodation by inhibiting the action of cholinesterase, or actually destroying it, that is, by an indirect-stimulatory mechanism. Anticholinesterase activity is the principal mode of action of physostigmine, diisopropyl fluorophosphate, and neostigmine. These indirect-stimulatory drugs require the presence of an intact nervous system to be effective. An iris and ciliary muscles damaged by recurrent acute bouts of elevated tension, therefore, may respond poorly to these compounds.

To know whether a miotic acts directly on the iris sphincter or whether it acts indirectly, by inhibiting cholinesterase, is helpful in determining the circumstances of use of the various drugs. When a direct-stimulatory drug, like pilocarpine, is applied to an eye, it seems to combine with an intracellular "receptor" substance and thereby to effect contraction of the cell. The degree of miosis seems determined by the number of muscle cells effectively stimulated. Maximal miosis is not obtained until nearly all muscle cells are contracting. Furthermore, stimulated cells, in accordance with the "all-or-none law," do not seem capable of reacting to acetylcholine (nerve stimulation) or other drugs. This is manifested by the fact that in inducing miosis and accommodation pilocarpine also reduces pupillary reactions to light and the amplitude of accommodation. In effect, pilocarpine "competes" with the physiologically produced acetylcholine and thereby reduces reactivity of the iris sphincter and the muscles of accommodation not only to light and near vision, but also to anticholinesterase drugs, such as physostigmine and diisopropyl fluorophosphate. The clinical significance of this fact will be discussed later.

Onset of action of a direct-stimulatory drug, like pilocarpine, is insidious and causes little discomfort. The intensity of its effects can be established and maintained by how much of and how frequently the drug is applied. This is clinically important, for it permits the physician to keep the patient's refractive error reasonably constant by a regular dosage schedule. As the effects of pilocarpine wear off, there is a period

of diminished muscle tone, which is evidenced by hyporeactivity of the pupil to light. After administration of large doses of pilocarpine there may even be a period of slight mydriasis. Contraction of the muscles of accommodation induced by pilocarpine is proportionately less than the miosis. With small doses of pilocarpine, it is possible, therefore, to induce a considerable degree of miosis with little disturbance in the refractive error. Finally, pilocarpine has little effect on the chemistry of the ocular fluids and does not influence the tone of skeletal muscle. These characteristics of directly acting miotics are highly desirable for a drug which is to be used in the treatment of chronic glaucoma, particularly in younger patients. It means that the drug can be used for prolonged periods without discomfort, variable changes in refractive error, alterations in the metabolism of the eye, or twitching of the skeletal muscles of the lid.

Of the directly acting miotics, pilocarpine is still the most useful for treatment of the chronic types of glaucoma. Its salts are relatively stable in aqueous solution; they consistently penetrate the cornea and seldom are allergens. Both the nitrate and the hydrochloride salts are well tolerated, but the former seems more stable and less irritating to the conjunctiva. More consistent absorption of pilocarpine can be obtained by adding a 0.5 to 1% of methylcellulose (4,000-centipoise type) to the solution.[3] This makes the solution more viscid, so that it is retained in the conjunctival sac for longer periods. Buffered solutions of pilocarpine and methylcellulose are quite nonirritating.

The action of pilocarpine is not prolonged; consequently, maintenance of consistent effects requires at least two instillations a day. This relatively short action may seem a disadvantage; however, it thus eliminates undesirable accumulative effects (unless the drug is administered more frequently than every six hours). A 3% solution is generally considered the maximal concentration which is consistently effective. In a review of the records of more than 100 patients whose ocular tension was uncontrolled with 2 or 3% solutions of pilocarpine nitrate, only 2 were found whose ocular tension persistently was controlled with 4% solutions.

Among the choline esters, carbachol is the only drug with sufficiently prolonged action that its use is practical in the treatment of chronic glaucoma. Methacholine iontophoresis is of value in the treatment of acute glaucoma or in the rupture of peripheral synechia in an occasional chronic case, but its action is too evanescent to maintain consistent miosis for an appreciable period.

Carbachol has a far more potent miotic and hypotensive action than have pilocarpine salts in comparable doses.[4] Its effects, moreover, are considerably more prolonged. The drug, however, has several disadvantages which largely limit its use to patients whose tension cannot be controlled by pilocarpine. Whereas pilocarpine salts can be administered effectively in simple aqueous solutions, carbachol requires both a special vehicle and an intelligent and cooperative patient who will take the necessary precautions to insure its absorption. Like other choline esters, it has a high affinity for water; consequently, when administered in simple aqueous solutions

3. Swan, K. C.: Use of Methyl Cellulose in Ophthalmology, Arch. Ophth. **33**:378-380 (May) 1945.

4. Swan, K. C.: Ocular Effects of the Choline Esters, Arch. Ophth. **42**:709-725 (Dec.) 1949.

it has a much higher affinity for the vehicle than the epithelium. As a result, relatively little penetrates the normal cornea. When administered in a dry suspension in an anhydrous base, the drug has a greater affinity for the epithelium than for the vehicle and, therefore, effectively penetrates the cornea. Immediate obscuration of vision by the ointment provides the patient with the assurance that the drug has definitely come in contact with the cornea and that he has instilled it adequately. Gentle massaging of the cornea through the lids further insures absorption.

Carbachol has prolonged and potent effects; therefore, it is capable of producing systemic symptoms when excessive doses are administered to the eye, or even with the usual dose if the permeability of the epithelial barrier of the conjunctiva and cornea has been reduced, either by topical anesthesia or by the instrumentation of tonometry. The epithelium is the main barrier to the penetration of carbachol. If it is disturbed, penetration of the drug is tremendously increased, and enough systemic absorption may occur to effect a decided drop in blood pressure and other symptoms due to generalized cholinergic stimulation. In summary, carbachol is a valuable drug to have in reserve for the treatment of advanced chronic glaucoma of the noninflammatory types. There are many patients with advanced glaucoma whose tension cannot be controlled by other drugs and for whom surgery seems inadvisable. Carbachol often prevents blindness in patients of this type, but the ophthalmologist must prescribe it judiciously, and the patient must take precautions to insure its proper absorption.

The type of contraction of the ocular muscles induced by indirectly acting drugs, such as physostigmine and diisopropyl fluorophosphate, is strikingly different. The onset of contraction is apt to be abrupt and violent. These drugs incite a hyperreactivity of this reflex because they protect physiologically produced acetylcholine from destruction and allow it to accumulate in the tissues, in contrast to the action of the pilocarpine, which reduces reactivity of the pupil to light. As a result, patients using these drugs may have painful spasms of the iris when they are passing from darkness into light. Disturbing spasms of accommodation, also, may result from attempted close work. Finally, these drugs increase the tonus of skeletal muscles; consequently, an annoying twitching of the lids may follow topical applications to the conjunctival sac.

In summary, the onset of action of direct stimulatory miotics, like pilocarpine, is gradual in onset, and intensity can be controlled by regular dosage. Reactivity of the intraocular muscles is reduced. These drugs are, therefore, nearly ideal in maintaining miosis for long periods in phakic patients with chronic glaucoma. On the other hand, the indirectly acting drugs, such as diisopropyl fluorophosphate, have a more violent, spastic action, of variable onset and intensity, associated with hyperreactivity of the ocular muscles and increased tonus of the skeletal muscles of the lids. In aphakic patients these effects are less noticeable, but in other patients the discomfort and disturbance in vision limit their use in chronic glaucoma to special circumstances, which will be discussed later.

A number of drugs induce miosis and cyclotonia by blocking the action of the cholinesterase; however, the only two which have received wide use in the treatment of glaucoma are physostigmine and diisopropyl fluorophosphate. They differ in their mode of action. Physostigmine seems to bind cholinesterase, as well as block

its action, whereas diisopropyl fluorophosphate actually destroys the enzyme. Its effects, therefore, are much more prolonged, and in comparable doses far more intense. In the normal eyes of a young patient a single instillation of 0.1% diisopropyl fluorophosphate will induce miosis and hyperreactivity of the pupil lasting many days.

Both physostigmine and diisopropyl fluorophosphate are relatively unstable in water; therefore they are best prescribed in an oily or an anhydrous vehicle. Physostigmine salicylate is most commonly used in 0.25% concentration in an oil base. Diisopropyl fluorophosphate is distributed in a peanut oil, but can be obtained in sesame oil if the patient acquires hypersensitivity to peanut oil.

Physostigmine is seldom used in chronic glaucoma except to control an occasional acute rise in tension. At the pH of the intraocular tissues it largely exists

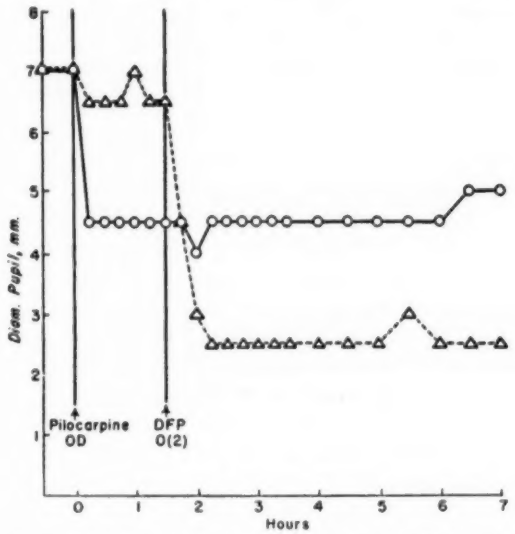


Chart 3.—Degree and duration of miosis induced by diisopropyl fluorophosphate (DFP) and diisopropyl fluorophosphate and pilocarpine nitrate. The values for 4% pilocarpine nitrate and 0.1% diisopropyl fluorophosphate, used in the right eye are shown by the line with circles; the values for 0.1% diisopropyl fluorophosphate, used in the left eye, by the line with triangles.

as a free base which is tissue-irritant. Its prolonged use may result, therefore, in a chemical iritis. Diisopropyl fluorophosphate has greater usefulness in chronic glaucoma. As has been stressed previously, the variable intensity and spastic nature of its action, along with hyperreactivity of the intraocular muscles, prevent its routine use in the treatment of chronic glaucoma in phakic patients. In the absence of the lens, pronounced disturbances in vision do not occur when the ciliary muscle is stimulated. Moreover, the pain and discomfort of iris spasm seem less. It is in the management of chronic glaucoma in aphakic patients, therefore, that diisopropyl fluorophosphate plays its most important role.

Combinations of miotic drugs commonly have been prescribed with the hope of obtaining more intense miosis and hypotensive effects than could be achieved by

prescription of a single drug. For example, it has generally been assumed that pilocarpine and physostigmine would have an additive effect because they have different modes of action. When methacholine and physostigmine were combined, true synergism was expected because the physostigmine prevents destruction of methacholine by the cholinesterase and thereby prolongs its action. It seems, however, that the capacity of the iris and the ciliary body to react to drug stimulation is limited and that the limit of reactivity can be reached by currently available drugs administered singly. In actual practice, therefore, additive and synergistic effects of miotic combinations are manifest only when submaximal doses are given. In fact, the intense spastic effects of diisopropyl fluorophosphate may be reduced appreciably by prior administration of large doses of pilocarpine. This "competitive," rather than "additive," action of certain miotics has been demonstrated in experimental animals (Chart 3), as well as in patients with acute glaucoma in whom it was possible to compare treatment in the two eyes.[5] In these patients combinations of pilocarpine and physostigmine have seemed less effective than maximal doses of physostigmine administered singly, although more effective than pilocarpine alone. A similar "competitive" relation exists between certain anticholinesterase drugs. Leopold and McDonald pointed out that at the same time that physostigmine binds and inhibits the cholinesterases, it also protects these esterases against the destructive action of diisopropyl fluorophosphate; therefore, diisopropyl fluorophosphate has less prolonged effects when given in combination with physostigmine.[6]

There are several possible clinical applications of this concept of competition between drugs. For example, in the initial medical treatment of acute glaucoma of the narrow-angle, iris-block types, administration of maximal doses of physostigmine or diisopropyl fluorophosphate singly could be expected to be more effective than the use of either drug combined with pilocarpine. In the treatment of chronic types of glaucoma different circumstances prevail. The intense spastic action and hyperreactivity of the intraocular muscles induced with diisopropyl fluorophosphate are very discomforting. These effects are much less severe if the patient has been receiving large doses of pilocarpine because reactivity of the intraocular muscles has been reduced appreciably; that is, prior administration of pilocarpine makes the initial application of diisopropyl fluorophosphate more tolerable. The discomforting effects of diisopropyl fluorophosphate usually disappear once the maximal effects of the drug are reached and maintained for a few days. Then pilocarpine can be discontinued by gradually reducing the dose. This technique permits the use of diisopropyl fluorophosphate in phakic patients with advanced glaucoma which has not responded to other miotics and when surgery is contraindicated. Diisopropyl fluorophosphate may also be used as a "booster" when pilocarpine therapy is not quite effective. For example, administration of 1 drop of 0.1 or 0.05% diisopropyl fluorophosphate every few days may sufficiently enhance the effects of the pilocarpine that the tension can be controlled.

In the above discussion, the ocular pharmacology of the miotic drugs has been reviewed. The choice of drugs and the dose to be administered to a given patient

5. Swan, K. C., and Gehrsitz, L.: Competitive Action of Miotics on the Iris Sphincter, A. M. A. Arch. Ophth. **46**:477-481 (Nov.) 1951.

6. Leopold, I. H., and McDonald, P. R.: Di-Isopropyl Fluorophosphate (DFP) in the Treatment of Glaucoma: Further Observations, Arch. Ophth. **40**:176-188 (Aug.) 1948.

depend on the aims of therapy and on the circumstances of the case, as well as on the mechanism of action of the drug. Miotic therapy of chronic glaucoma, particularly of the secondary types, is no longer directed solely toward control of the ocular tension with the minimal effective dose. For example, there are many types of chronic glaucoma which are definitely the result of obstruction of the chamber angle, either by apposition of the iris with the cornea or by anterior peripheral synechia. Gonioscopic examinations demonstrate that in many patients it is possible to rupture newly formed adhesions by use of strong miotics and thereby to reopen the chamber angle, in a manner nearly comparable to that of breaking a posterior synechia of delicate or recent formation with mydriatics and thereby to free the pupil.

There are several circumstances under which anterior peripheral synechia develops. Its formation is predictable to a certain extent, therefore, except in the case of glaucoma due to vitreous block; elevations in tension developing weeks or months after a cataract extraction are almost invariably due to peripheral synechia. This, in turn, results from prolonged apposition of the iris with the cornea, the adhesion developing first in the area of the healing incision. The patient who has had a shallow chamber after operation should be particularly suspected of having peripheral adhesions, and gonioscopic examination should be undertaken as soon as healing of the wound makes it safe. This is usually three to five weeks after operation. If adhesions are seen to be developing, or even if the peripheral iris is observed to be in apposition with the cornea, miotics should be administered, in an attempt to free the angle. This should be done as a preventive measure even if the ocular tension is normal. A second common circumstance favoring development of peripheral synechia is the use of mydriatic drugs for prolonged periods in treatment of iridocyclitis. Wide dilation of the pupil and inflammation of the iris favor its formation. In all patients with such a condition requiring prolonged mydriatic therapy, treatment should be discontinued for short periods to mobilize the peripheral iris. If peripheral adhesions appear, miotic therapy should be begun early in the postinflammatory period. To wait until these adhesions are firmly organized and glaucoma has developed is to lessen appreciably the possibility of a favorable outcome. Still another circumstance in which peripheral synechia develops is the narrow-angle type of chronic glaucoma. In patients so affected, particularly those with intumescence of the lens, the iris is likely to be in close apposition with the cornea for prolonged periods. Adhesions may form in such eyes when they are treated with the minimal doses of pilocarpine necessary to control the tension. A gradual rise in tension may then develop. This is not due, as was formerly thought, to the development of tolerance to the drug, but, rather, is caused by progressive obstruction of the chamber angle. If such eyes are treated from time to time with diisopropyl fluorophosphate or methacholine by iontophoresis in order to effect a tremendous pull in the iris root, a marked drop in tension may occur, and it is found that the tension again can be maintained with relatively small doses of pilocarpine. In fact, in every case in which chronic glaucoma is diagnosed, it seems a wise policy to have a period of treatment with strong miotics in order to free the chamber angle as much as possible before starting maintenance therapy.

It has long been recognized that there are individual differences in tolerance of the eye to abnormal ocular tension; therefore, evaluation of the effectiveness of

therapy has been based upon studies of visual function, as well as on tonometric determinations, as tabulated.

1. Ocular tension
   (*a*) Base level
   (*b*) Intradiem fluctuations
2. Functional studies
   (*a*) Visual fields and acuity
   (*b*) Dark adaptation
3. Progression of associated pathology, e. g., peripheral anterior synechia

Loss of visual field in cases of chronic glaucoma is generally permanent; therefore, we have sought additional criteria for judging the efficacy of treatment. In recent years my colleagues and I have observed that development or progression of certain morphologic changes in the eye is almost invariably associated either with progressively high ocular tension or with visual impairment which may require a change in medical treatment or surgical intervention or both. Some of these morphologic changes may contribute to the difficulties of controlling

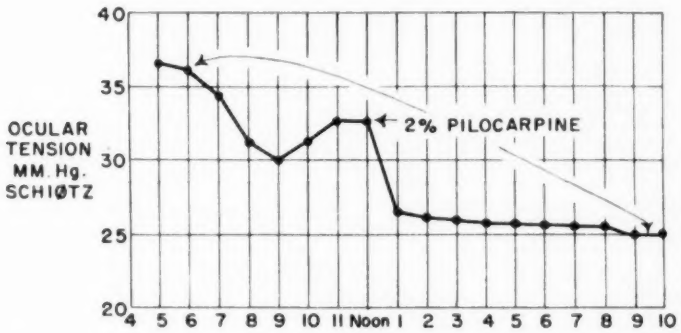


Chart 4.—Intradiem tension curve for 34 eyes treated with pilocarpine, representing an average of 721 tonometric determinations.

ocular tension. Formation of peripheral synechia has already been mentioned. Progressive enlargement of the lens, with resultant encroachment on the chamber angle, is another of the commoner factors contributing to the seeming progress in the glaucomatous process. Other morphologic changes are primarily degenerative and seem indicative of poor tolerance of the eye to the increased intraocular pressure. Alterations in and around the optic disk are the cardinal examples. These may develop or progress without measurable changes in the visual field. Finally, morphologic changes may occur which do not seem either to contribute to the elevation of the tension or to be a direct result of it; nevertheless, they must be considered in decisions concerning treatment. For example, one cause of severe visual loss in chronic glaucoma is occlusion of a retinal vein where it is compressed in crossing the edge of a glaucomatous cup.

Regular determinations of visual function remain an important part of the evaluation of treatment in patients with chronic glaucoma. Impairment in dark adaptation occurs in these patients; therefore, it has become the custom at the

University of Oregon to produce dark adaptation in such patients and to study the visual field in relatively low illumination. This procedure has resulted in more consistent findings and in detection of slighter defects than was possible with previous techniques.

Tonometric measurements are made more frequently than visual field studies, and on an intradiem basis. Frequently it has been found that the tension is elevated during the early hours of the morning when afternoon determinations on the same patient give normal limits. If the ocular tension had been determined in such patients only during the clinic hours, a diagnosis of so-called low-tension glaucoma would often have been made (Chart 4). The term "intradiem tension curve" may imply that multiple determinations of the tension are made during the same day on a given patient, but in practice intradiem variations seem best established by determinations made on different days and hours. A more adequate sample of the patient's variations in tension in the ordinary circumstances of his living is obtained, and his ability to instill his own medication can be evaluated. In establishment of dosage schedules, an effort is made to avoid fluctuations in ocular tension during the day and to keep the ocular tension at low levels throughout the 24-hour period.

*Causes of Failure in Medical Treatment of Eighty-Four Patients with Chronic Glaucoma*

| | No. of Patients |
|---|---|
| Misdiagnosis | 9 |
| Inadequate or improper prescription | 16 |
| Patient misunderstanding | 18 |
| Medical treatment impractical | 4 |
| Progression of associated pathology | 16 |
| Unknown | 21 |

In general, if the patient's base level of ocular tension is high, the concentration of the drug solution is increased. If rises in tension occur between instillations, frequency of administration is increased.

The physician must not be satisfied simply to establish what seems to be a satisfactory intradiem tension curve. He must consider, also, how high the tension might rise. In an occasional patient repeated tonometric determinations may indicate that, although the tension is generally maintained at a low level, occasionally abrupt rises in tension occur. Such a patient has the potentialities for the development of acute glaucoma and may need only a missed drop, an emotional upset, or an excessive fluid intake to precipitate an attack which may seriously damage his eye. When such a potentiality is suspected, provocative tests should be undertaken and treatment modified in accordance with the results. Usually, a simple peripheral iridectomy suffices. Miotic therapy generally has to be continued after operation, but the patient is relieved of the risk of an attack of acute glaucoma which might have destroyed his vision.

It seems important to stress that the scientific side of treatment is but one part of the management of patients with chronic glaucoma. Under the sponsorship of the Kellogg Foundation, Dr. Leonard Christensen and I have been studying the circumstances leading to loss of vision in chronic glaucoma. Causes of failure of medical therapy were reviewed in 84 consecutive patients referred for glaucoma surgery (Table). Inadequate or improper prescription of miotics was the basis of visual

loss in 16 patients. For most of these patients miotics had been prescribed without a clearly defined schedule of administration. As a result, these patients used their medication only when it suited their convenience and generally neglected the important night and early morning doses. An additional group, of 18 patients, discontinued medical treatment because they did not understand its aims. Some had suffered discomfort, or even a blurring of visual acuity, from the miotics and thought, therefore, that the prescription was improper. Others had expected improvement in vision and became discouraged when they did not see better after using the medication a few weeks. This study will be reported in detail elsewhere, but it signifies that a certain amount of the "art of medicine" is essential to the proper management of the patient with chronic glaucoma.

## SUMMARY

There are drugs, like dibenamine,* which induce miosis by relaxation of the iris dilator (paralytic miosis), but these drugs are effective only by systemic administration. They may effect a dramatic drop of an ocular tension which is useful in the emergency control of certain types of acute glaucoma. They demonstrate, also, the feasibility of at least temporarily reducing ocular tension by depressing formation of the aqueous; however, present medical treatment of chronic glaucoma is primarily with drugs which stimulate the iris sphincter and the muscles of accommodation. Whether a stimulating miotic acts directly on the muscle cells, or indirectly, by inhibiting cholinesterase, largely determines the circumstances of its use in the treatment of chronic glaucoma.

Directly acting drugs, such as pilocarpine, reduce reactivity of the intraocular muscles and have little or no effect on the skeletal muscles or the chemistry of the intraocular fluids. These drugs are insidious in the onset of their action. The intensity of their effect, also, can be maintained at a constant level. For these reasons, directly acting drugs can be used for prolonged periods with little disturbance in vision or discomfort and have features nearly ideal in the treatment of chronic glaucoma. In contrast, indirectly acting miotics, like diisopropyl fluorophosphate, have a violent and variable intensity of action. Moreover, they induce hyperreactivity of the pupil, the accommodative mechanism, and the skeletal muscles of the lid. These characteristics limit their use in the treatment of chronic glaucoma to special circumstances. For example, these disturbing effects are less pronounced in the absence of the lens, and therefore these drugs have their greatest usefulness in chronic glaucoma in aphakic patients.

Reactivity of the intraocular muscles to drugs is limited, and the limit can be reached by miotics administered singly. For this reason, additive and synergistic effects of drugs are manifest only when administered in submaximal doses. Otherwise drugs seem to "compete." The effects of diisopropyl fluorophosphate can be shortened by prior administration of physostigmine, which protects the cholinesterase from destruction by diisopropyl fluorophosphate. Moreover, the intense and violent action of diisopropyl fluorophosphate and physostigmine on the iris sphincter can be modified and made more tolerable by the previous administration of pilocarpine in doses sufficient to reduce reactivity of the muscle cells.

Miotic therapy of chronic glaucoma is no longer purely symptomatic. The types secondary to obstruction of the chamber angles can often be prevented, or even

cured, by miosis sufficiently intense to disrupt peripheral adhesions. Keeping the chamber angle open by occasional induction of intense miosis is important because adhesions tend to form in all types of chronic glaucoma. In evaluation of miotic therapy, dependence should not be placed solely on determination of the ocular tension and visual function. Development or progression of certain morphologic changes in the eye may indicate the need for a change in therapy before irreparable loss of vision occurs.

Repeated determinations of the tension on different days and at different hours seem essential to establish an adequate dosage schedule. Many patients with so-called low-tension glaucoma have been found to have abnormally elevated tensions during the night, and other patients have been found to have periodic acute rises in ocular tension while the glaucoma was seemingly well controlled. In additional studies of causes of failure of medical treatment, it was found that poor psychologic management of the patient and improper prescription were important factors.

# CLINICAL TESTING OF VISUAL ACUITY

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THE MOST exhausting activity in the practice of an ophthalmologist is to persuade persons to read the normal line of the visual test chart. Complicated operations and intricate diagnostic problems sometimes seem next to nothing in comparison; but why this keen interest?

Examination of the visual acuity is classified as a subjective test, but in certain circumstances the answers are as sure as objective results. The moment the patient is brought to read the normal line, it is proved with the exactitude of an objective method that the visual acuity of the examined person is normal, and the whole test then changes from a doubtful to an exact one. This result is worth while.

The next question to be discussed is, of course, the normal value for the visual acuity. Ability to recognize letters of 5 minute angle is generally recognized as normal, corresponding to a visual acuity of 1.0 or 20/20, or 6/6.

I tested the visual acuity of 100 Danes, chosen at random and of different ages. From a distance of 12 meters, the subject approached the visual test chart gradually until the 6-meter line could be recognized, with only one wrong answer to three correct ones. In the accompanying chart the abscissa indicates letters on the test chart. The ordinate indicates the number of persons able to achieve the corresponding visual acuity. The curve has its peak at a visual acuity of 1.17, or 7/6, or 23/20. Visual acuity of 1.0, or 20/20, or 6/6 is found at the dot in the left side of the curve, rather low.

What point in this curve for visual acuities is to be selected as a normal value, suitable for clinical use?

The right arm of the curve represents the best visual acuities, but these optimal values are seldom of clinical interest. The peak of the curve represents the mean. This is of great biological interest; but for clinical purposes, when one is examining a particular person and judging his condition, the mean value is of limited interest, since half of mankind would be found inferior if the mean were fixed as the norm. Theoretically, the best clinical normal value should be fixed on the left arm of the curve, at the point where the slope is most abrupt. A norm fixed where the curve changes its course, forming a foot, would secure to the greatest number of persons with normal vision their being declared normal on the test. At the same time, this norm would exclude the fewest persons with a minus variation of the normal visual acuity, as the normal persons with visual acuity below the fixed norm are very few (the area of the curve to the left of the arrow). Thus, values below this clinical norm are, in all probability, really abnormal. It is astonishing to

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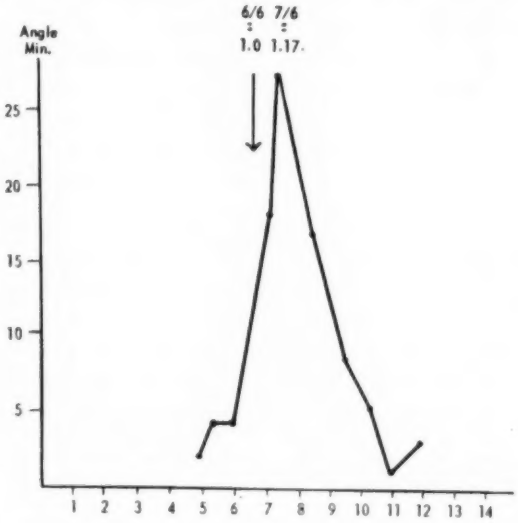
see how precisely this theoretical point is attained by experience in the generally used Snellen norm, fixed at a visual angle of 5 minutes.

When a child begins school and has learned the letters, a reader with letters of large size is generally used. As normal children have good visual acuity and good accommodation, far exceeding what is needed to read ordinary print, it seems quite unnecessary for visual reasons to print the letters in the readers so large. But such large letters are urgently needed. For some reason, utilization of the form sense for small visual angles produces great strain, and, of course, is especially tiring in the case of abstract figures when presented to untrained observers.

That the sense of form is easier to utilize at a large visual angle than at a small one is curious, but is clearly apparent from the much shorter time needed to




Curve showing vision of normal persons.

recognize a letter when the visual angle is increased. By increasing the visual angle from 5 to 10 minutes, I found that the time necessary to recognize the same letter diminished from $\frac{1}{2}$ to $\frac{1}{20}$ second. That means that a doubling of the visual angle for a given form under these conditions increases the visual velocity 10 times.[1]

When one is teaching a child his letters, it is the custom to present at the beginning only a few letters on each page. This is because of another characteristic property of the eyesight. The sense of form is most easily utilized in an otherwise empty visual field. When one is testing amblyopic children with isolated letters or E's, the visual acuity recorded is often much better than with the ordinary test chart. If the visual field is crowded with letters, the area of the visual field in which the letters can be recognized narrows. This is very easy to demonstrate, as I showed at the Congress of Scandinavian Ophthalmologists in 1936.[2]

1. Ehlers, H.: On Visual Velocity, read at the Eleventh Ophthalmological Congress of Scandinavian Ophthalmologists, June 26, 1947, Acta ophth. **26**:115, 1948.

2. Ehlers, H.: Movements of Eye During Reading, Acta ophth. **14**:56, 1936.

The eyes, thus, are not always able to utilize the form sense maximally. The reading of the normal line crowded with many letters seen under a small visual angle is to many persons real strain.

The problem of the correct gradation of our test charts and the true manner of expressing the visual acuity has often been discussed, some oculists preferring the decimal system and others the simple fractions. Of the latter, some express the fractions in a quasiduodecimal system and measure the distances in the metric system; for others 20 ft. form the basis. This heterogeneity is unfortunate.

A general law for all units of measurements is that the steps of the scale must exceed the error on any value determined; otherwise it is impossible to interpret the results without complex calculations. For the testing of visual acuity, this means that the gradation of the test chart, i. e., the number of steps between the lines, is dependent on the physiology of the eye. If the ability to read the letters presented shows an error of 1/7, the charts must be divided into seven intervals. There is no possibility of dividing them into more than seven steps without diminishing the accuracy of the visual test. As test charts divided according to this system approximately correspond with series somewhat resembling geometric or logarithmic ones, gradations of the latter type have been proposed (Green, Javal, Tscherning). To me, it is not a problem of numerical systems or of mathematics, but merely one of what an eye is able to discriminate.

Persons reading without error a line of good visual acuity generally are able, by straining, to read one of the easiest letters in the next line too; this is a simple and good proof that the intervals between the steps of the test chart are as they ought to be, just at the limit of the error in the test.

Form vision is a complex sense, composed, as it is, of a number of visual functions. In most organic diseases of the eye disturbing the formation, resolution, or transmission of the visual image, all the various functions are reduced. As the various visual functions often go together, the visual test may usually be restricted to the testing of the form sense, which is the simplest to perform. Only in special cases is it necessary to supplement the examination by testing other visual functions to get a true picture of the visual impairment.

It is generally assumed, but is not quite true, that the visual acuity test is an examination of the sense of form. According to Snellen, the letters should be shaped so that each point is recognized separately from the others at equal distances. Actually, this is an examination of the resolving power, dependent on the light sense. The recognition of figures of varying complexity, but of equal size, would be a pure form-sense test. Curiously, this ability is dependent on the visual angle.

What further complicates the separation of the different visual functions is the particular fact that the sense of form, owing to its simplicity, frequently is used as a sort of indicator in testing light sense or color sense, as, for instance, in the Ishihara test.

To demonstrate how often the ability to distinguish different intensities of light and the ability to distinguish different sizes go together when vision decreases, I may refer to some investigations I reported in 1937,[3] at the Congress of Ophthalmologists in northwestern Germany. The power of distinguishing gray shades was measured by means of pale letters printed in different intensities of gray, from

3. Ehlers, H.: Ein tausend Hemeralopieuntersuchungen, Acta ophth. **15**:443, 1937.

pale gray to dark, after the method of Edmund and Möller. These letters were presented under various reductions of illumination. The reduction of the form sense and that of the light sense were found to be associated in many ocular diseases.

Although the reductions in the various visual functions generally go together, isolated defects of a single function occur, too, as is typically the case in color blindness. The form sense is unimpaired, and so is the light sense. Isolated defects of the light sense are well known, too, in real day blindness. In such cases the ordinary visual test does not express the actual visual reduction. The reverse is the case in isolated reduction of the form sense; the visual acuity test will give the impression of a far more serious condition than the actual one.

The typical picture of the isolated reduction in form sense is seen in amblyopia without organic changes. The patient with the amblyopic eye may indicate exactly when the right correcting glass is placed in front of his eye, even when the visual acuity is severely reduced, and even when his visual acuity does not improve with the glass. This is due to an unimpaired light sense, which enables the patient to perceive the feeblest circles of diffusion on the retina. I have examined the power of distinguishing light intensities, and I always find that this function, as well as the visual velocity, are excellent in cases of amblyopia.

A patient with an amblyopic eye often is not aware of his defect until it is revealed at the visual test. A patient may come for presbyopic glasses without knowledge of the amblyopia and is astonished, just as is a dichromate, when his defect is revealed. When such a patient is questioned, he states that things seem very bright and clear to the amblyopic eye, but, as a colleague added, "I don't understand so well what I see with my clumsy eye." For guidance an amblyopic eye may be excellent. I remember a foreigner's desiring to get a Danish driving license. The man had only one eye, and it had an acuity of 20/200. I was questioned by the police, who stated that the man drove his car excellently but could not see to read the traffic placards. As the man did not understand Danish either, I thought it made no difference.

I have tried to emphasize that the visual acuity of an amblyopic eye does not indicate the same degree of disability as the same visual acuity found in an eye with organic disease. The two conditions cannot be compared. The treatment for amblyopia seems less glorious when this is appreciated.

Many different methods and instruments have been devised for testing visual acuity. Nearly every clinic has its favorite. It is impossible to say which is the best, for a person's visual acuity does not have one true value. In the same person the visual acuity may vary somewhat, depending on ocular and general conditions. The aberrations cause circles of diffusion and of these it seems possible for the eye to choose now one, now another. Within the same pupil the refraction may vary in different parts by several diopters, as a result of the aberrations, as demonstrated by my compatriot Tscherning. So there cannot be one true value only for the visual acuity of an eye. When discussing what gives the best vision, we should not forget that the owner of the eye is the one best fitted to decide.

# FUNDUS PHOTOGRAPHS IN COLOR USING A HIGH-SPEED FLASH TUBE IN THE ZEISS RETINAL CAMERA

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ONE HESITATES to publish another paper on a modification of the Zeiss-Nordenson retinal camera for obtaining fundus photographs in color. A number of papers on such modifications have appeared in recent years.[1] There is, furthermore, now obtainable commercially a new retinal camera for such photography which is proving popular. However, we believe that the modification to be reported here, in which a high-speed flash tube is used to provide the light, has advantages over any modification heretofore described.

By using again the ring of light just within the pupil to illuminate the retina, and photographing directly through the center of the pupil, one can obtain pictures which are reflex-free. Because the flash exposure of this tube is of the order of 0.0001 second, the problems of blinking and of the movements of the eye being photographed are eliminated. The use of the flash-tube technique also is less fatiguing and annoying to the patient.

## METHOD

The improvement was made on the second model of the Zeiss-Nordenson camera, in which a filament incandescent lamp replaced the carbon-arc lamp of the earlier model. The entire filament-lamp housing unit, including the heat filters and shutter, was removed. Substituted was a new unit built to house a helical-type photo flash tube ("Amglo R 9 M").[2] Figure 1 shows schematically the assembly. The helical flash tube is oriented in its housing so that the axis of the helix coincides with the axis of the camera. A suitable lens system forms an image of the end coil, which will not only be situated at the mirror ($M$) but will also be the same size as the image of the filament used in the original camera. The image of this "circle" of light replaces that of the circular coil of the original filament lamp. The final image of the coil when placed in the plane of the entrance pupil of the eye to be photographed will be the same as that of the filament in the original camera. Thus, the fundamental optical system of the camera is left unchanged. All lens surfaces were coated to reduce loss of light due to reflection.

1. Mann, W. A., Jr.: Color Photography of the Fundus Oculi: Description of a New Method, Arch. Ophth. **8**:405-408 (Sept.) 1932. Koch, F. L. P.: Color Photography of the Human Ocular Fundus: Its Technic with the Zeiss-Nordenson Retinal Camera, J. Biol. Photographic A. **9**:119-135 (March) 1941. Bogart, D. W.: Kodacolor Fundus Prints: A New Technic, Arch Ophth. **29**:278-281 (Feb.) 1943. Tower, P.: Color Photography of the Eyeground: Report of an Improved Technic, ibid. **43**:1074-1079 (June) 1950.

2. Manufactured by the Amglo Corporation, Chicago.

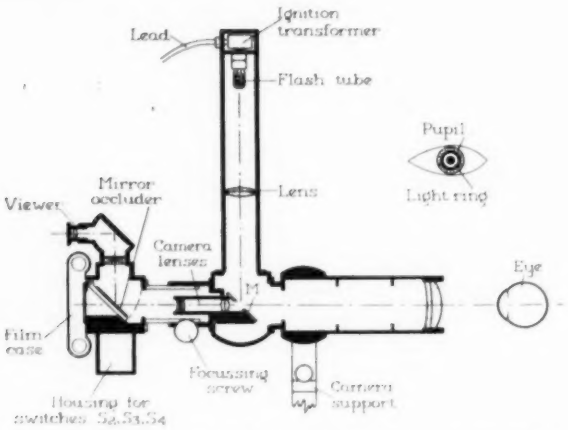


Fig. 1.—Schematic drawing of modified Zeiss retinal camera showing the flash-tube assembly. Reproduced with permission from Jacobs and Ogle.[3]

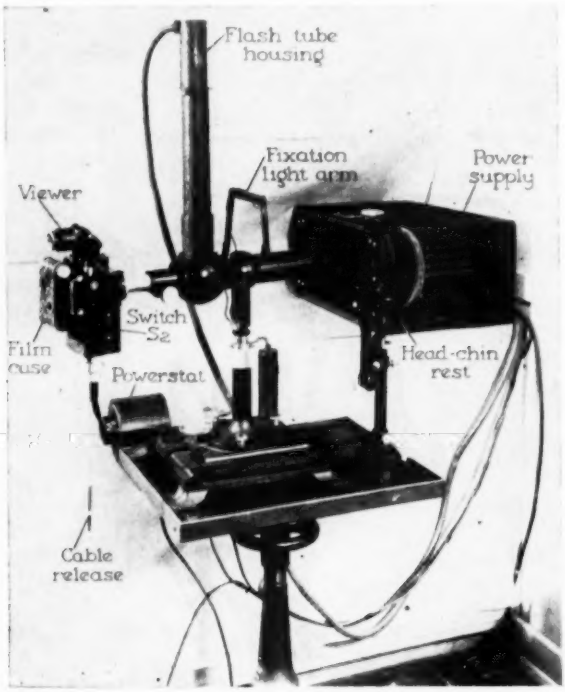


Fig. 2.—Photograph of the retinal camera with flash-tube attachment. Reproduced with permission from Jacobs and Ogle.[3]

During the adjustment and focusing of the camera (modeling) prior to the taking of the photograph, the flash tube is multiply flashed at a lower intensity at a rate of about 40 flashes per second. The intensity of the modeling flashes can be varied by a suitable powerstat. The fact that this modeling light is flashing does not interfere with the adjustment and focusing of the camera preparatory for the photograph. The mirror-occluder plate, immediately in front of the film holder, protects the film from light during the modeling period. At the moment a photograph is to be made, pressure on a cable release successively stops the modeling light flashes, raises the mirror-occluder plane, and then triggers the flash tube for maximal intensity. The special electronic and electrical circuits which are necessary for this procedure have been described fully elsewhere.[3]

The film housing had to be completely rebuilt so that commercial No. 120 film could be used. This necessitated increasing the focal length of the camera lens by about 1 in. (2.5 cm.), and for this a small diverging lens was attached to the camera lens system. A spacer was also necessary to increase the distance of the viewing eyepiece. This change in focal length of the system increased somewhat the magnification of the picture, but this is proving to be an advantage. Because a larger overall picture is obtained, there is little loss in the retinal area covered.

It was found that with the flash tube used at maximal efficiency there was still not enough light for use with kodachrome® color film. However, experiment showed that ektachrome® daylight film could be used with very satisfactory results if that film was overdeveloped by about two and a half times to compensate for the underexposure. Such overdevelopment would ordinarily tend to intensify the red in the film when exposed to incandescent light sources. However, the light from the flash tube is rich in the blue, and since the dominant color of the fundus is red, the resultant transparencies appear to reproduce very faithfully the color of the fundus.

A fixation light, the position of which can be adjusted, has also been added to the camera.

The result of this modification of the Zeiss retinal camera has produced unusually satisfactory pictures in that fine structures of the retinal vessels, small lesions, punctate hemorrhages, and small exudates are visible in the pictures. Eye movements and blinking of the eyelid are no longer problems. Disadvantages lie, first, in the fact that the pupils must be fully dilated, and second, that the film must be processed locally. It is highly probable that further improvements in the lamp and housing will even eliminate the necessity for local processing of the film.

Figure 2 is a photograph of the camera as modified for the flash-tube adaptation.

3. Jacobs, M., and Ogle, K. N.: Application of High-Speed Flash Tube to Photographing the Fundus of the Eye in Color, Rev. Scient. Instruments **24**:52-55 (Jan.) 1953.

# Ophthalmological Reviews

## AQUEOUS VEINS

### Their Status Eleven Years After Their Detection

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CINCINNATI

THE HUMAN eye is a unit consisting of an image-producing apparatus—cornea, aqueous humor, lens, and vitreous body—and an image-receiving apparatus, the retina. In order to function normally, this unit has to be properly protected, nourished, and kept under optimal conditions. Among these, nutritional and oxygen supply, adequate temperature and hydrogen ion concentration, elimination of waste products, and preservation of a normal intraocular pressure are of paramount importance.

The maintenance of normal intraocular pressure depends on the elasticity and rigidity of the ocular coats, i. e., sclera and cornea, and on the contents of the eyeball. These are composed of the intraocular fluids and tissues and the quantity of blood filling the vessels of the intraocular tissues, particularly the uvea.

All over the body, fluid may leave or enter capillaries according to the relative values of tissue pressure and intravascular pressure and of osmotic and colloidal osmotic pressure which prevail inside and outside the vessel walls. An individual capillary may yield tissue fluid in its proximal part and accept tissue fluid in its distal part. In the human eye, there is, superimposed on this universal water exchange through the capillary endothelium, a continuous gross circulation of fluid, with its source in the ciliary body and its goal in the chamber angle, as postulated by Leber.[1] From the angle of the anterior chamber fluid seeps through the trabecular meshwork into the canal of Schlemm, thence through the scleral venous meshwork, and, finally, into conjunctival and episcleral veins. This circulation of fluid, however, was never definitely proved to exist, or really observed. For decades many investigators denied the existence of a continuous production and elimination of intraocular fluid, as did Duke-Elder [2] 20 years ago. The detection of the aqueous veins, in May, 1941, confirmed Leber's theory and disproved the assumption of stagnation of the intraocular fluid. With a continuous flow of intraocular fluid leaving the canal of Schlemm through the aqueous veins,[3] a continuous production of aqueous humor is postulated.

This study was aided by a United States Public Health Grant (B-158).

Read before the Section on Ophthalmology at the One Hundred First Annual Session of the American Medical Association, Chicago, June 11, 1952.

1. Leber, T.: Die Circulations—und Ernährungsverhältnisse des Auges, in Handbuch der gesamten Augenheilkunde, edited by T. Saemisch, Leipzig, Wilhelm Engleman, 1903, Vol. 2.

2. Duke-Elder, W. S.: Text-Book of Ophthalmology: Vol. 1, The Development, Form, and Function of the Visual Apparatus, London, Henry Kimpton, 1932.

3. Ascher, K. W.: Aqueous Veins: Preliminary Note, Am. J. Ophth. **25**:31-38, 1942.

Aqueous veins (vasa efferentia humorem aqueum) are biomicroscopically visible channels resembling blood vessels and connecting the canal of Schlemm and its outlets into the deep scleral meshwork with the superficially visible conjunctival and episcleral vessels.

## QUALITIES AND CONTENTS OF THE AQUEOUS VEINS

Aqueous veins are to be recognized (*a*) by a pale, or even limpid, coloration, in contrast to the red of ordinary blood vessels; (*b*) sometimes by stratification, that is, a visible separation of the blood and the clear fluid into two or more layers running parallel to the vessel wall; (*c*) by their more or less characteristic origin, course, and emptying, and (*d*) by their typical response to certain experimental manipulations.[4]

With the use of the corneal microscope, these veins are found in practically every normal human eye, regardless of race, color, sex, or age; larger aqueous veins occur in about every third eye,[5] often symmetrically located in the right and left eye.[5] One, two, or more aqueous veins can be seen in a single eye. Larger aqueous veins can be detected with a 10 X magnifying loupe.[6] Although the structures surrounding the chamber angle of the animal eye differ markedly from the microanatomy of the human eye,[7] aqueous veins have been found and studied in eyes of rabbits and other animals.[8]

Aqueous veins in the human eye originate in or near the corneoscleral limbus, from the limbal meshwork, from an arch or a figure-6-like loop ascending out of the depth of the limbal tissue, or from a scleral emissary at some distance from the limbus.[5] The first type of origin yields the smallest and most superficially located aqueous veins, while aqueous veins deriving from a scleral emissary are the largest and most deeply located.

The length of aqueous veins is between a fraction of a millimeter and 1 cm. or slightly more.[5a] What appears to be a long aqueous vein is often a recipient vessel.

The width of aqueous veins is between that of a postcapillary conjunctival vein and that of the largest subconjunctival veins, or approximately between 0.01 and 0.1 mm.

The intravascular pressure of aqueous veins[9] is close to that of conjunctival veins, but it must remain slightly higher in order to allow continuous elimination

4. Ascher,[3] p. 33.

5. (*a*) Ascher, K. W.: Aqueous Veins: Physiologic Importance of the Visible Elimination of the Intraocular Fluid, Am. J. Ophth. **25**:1174-1209, 1942; (*b*) footnote 3.

6. Ascher, K. W.: Further Observations on Aqueous Veins, Am. J. Ophth. **29**:1373-1387, 1946.

7. Troncoso, M. U.: The Intrascleral Vascular Plexus and Its Relations to the Aqueous Outflow, Am. J. Ophth. **25**:1153-1162, 1942.

8. (*a*) Schmerl, E.: Significance of Action of Paredrine on the Ocular Tension of Rabbits, Am. J. Ophth. **30**:187-190, 1947. (*b*) Moreu, A.: La gonioscopia en el glaucoma, Arch. Soc. oftal. hispano-am. **8**:80-89, 1948. (*c*) Ascher, K. W.: Aqueous Veins and Contact Lenses, Acta XVI Conc. Ophth. London **1**:674-687, 1951; Am. J. Ophth. **35**:10-20 (May, Pt. 2) 1952. (*d*) Weekers, R., and Prijot, E.: Vasoconstriction des veines aqueuses et ophthalmotonus, Ophthalmologica **121**:264-274, 1951. (*e*) Wegner, W., and Intlekofer, W.: Klinische und experimentelle Beobachtungen an Kammerwasservenen, Klin. Monatsbl. Augenh. **120**:1-14, 1952.

9. (*a*) Thomassen, T. L.: The Venous Tension in Eyes Suffering from Simple Glaucoma, Acta ophth. **25**:221-241, 1947. (*b*) Löhlein, H., and Weigelin, E.: Über den Abfluss des Kammerwassers am normalen und glaukomkranken Auge, Ber. Versamml. deutsch. ophth.

*(Footnote continued on next page)*

of fluid into the recipient vessel. In normal eyes the intravascular pressure of aqueous veins is between 8 and 11 mm. Hg,[10] and it is not elevated in glaucoma.[9b]

The speed of current in aqueous veins is between 1 and 8 mm. per second; it varies from vein to vein, and also slightly from time to time in the individual vessel.[11]

The amount of aqueous humor leaving the canal of Schlemm as calculated from the number of, width of, and speed of, current in aqueous veins [5a] corresponds grossly to the figures arrived at, using various other experimental methods.[12]

The emptying of the aqueous veins into recipient vessels resembles that of a clear creek into a muddy river [13]; below the junction the aqueous and the sanguineous phase may continue to run in separated layers or may mingle. This stratification is due to differences between aqueous humor and blood in solid contents, in specific gravity, and in surface tension. Thorough mixing of blood and aqueous humor in the aqueous veins or the recipient vessels requires time and energy.[14] The pale or limpid color of aqueous veins is due to the presence in these vessels of aqueous humor, which may or may not be mixed with varying amounts of blood.[5]

Prolonged observation and photographs taken at intervals of several years [15] prove that the appearance of clear fluid in subconjunctival and conjunctival vessels is not a transient phenomenon; the same vessel is consistently charged with elimination of aqueous humor despite spontaneous or experimentally produced changes.[8]

Interest in the aqueous veins is growing; having survived their first lustrum as a near heresy, and their second lustrum as a curiosity, they have at last found almost universal recognition.[16] A few objections, however, have recently been made not so much to the existence as to the interpretation of the aqueous veins.

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Gesellsch. (1949) **55**:170-174, 1950. (*c*) Linnér, E.: Measurement of the Pressure in Schlemm's Canal and in the Anterior Chamber of the Human Eye, Experientia **5**:451-452, 1949. (*d*) Linnér, E.; Rickenbach, C., and Werner, H.: Comparative Measurements of Pressure in the Aqueous Veins and the Conjunctival Veins Using Different Methods, Acta ophth. **28**:469-478, 1950. (*e*) Rickenbach, K., and Werner, H.: Scheinbarer Abflussdruck, Tension und Druck in Kammerwasservenen, Ophthalmologica **120**:*22-27*, 1950. (*f*) Löhlein, H.: Die therapeutische Beeinflussung von episkleralem Venendruck und Abflussdruck des Kammerwassers im gesunden und glaukomkranken Auge, Ber. Versamml. deutsch. ophth. Gesellsch. (1950) **56**:146-151, 1951.

10. Löhlein and Weigelin.[9b] Linnér and others.[9d]

11. (*a*) de Vries, S.: De zichtbare afvoer van het kamerwater, Drukkerij Kinsbergen, Amsterdam, 1947, p. 75-76. (*b*) Kleinert, H.: Der sichtbare Abfluss des Kammerwassers in den epibulbären Venen, von Graefes Arch. Ophth. **152**:*278-299*, 1951.

12. Ross, E. J.: Circulation of Aqueous Humor and the Experimental Determination of Its Rate of Flow, Brit. J. Ophth. **36**:41-51, 1952.

13. Ascher,[3] p. 35.

14. (*a*) Gartner, S.: Blood Vessels of the Conjunctiva: Studies with High-Speed Macrophotography, Arch. Ophth. **32**:464-476, 1944. (*b*) Adler, F. H.: Physiology of the Eye: Clinical Application, St. Louis, C. V. Mosby Company, 1950, p. 270.

15. Ascher, K. W.: Search for Aqueous Veins, Correspondence, Am. J. Ophth. **31**:105-106, 1948.

16. Scheie, H. G.: Glaucoma: A Review of the Literature 1949-1950, Arch. Ophth. **44**:883-908, 1950; A Review of the Literature 1950-1951, ibid. **46**:677-709, 1951.

Up to now more than 120 papers dealing with, or discussing, the aqueous veins and 11 books referring to them have been published by American, British, Dutch, Swiss, Scandinavian, Belgian, Italian, French, Spanish, Greek, Austrian, German, Czech, and Hungarian authors.

Henderson [17] expressed the opinion that an aqueous vein is not a vein connected with Schlemm's canal but a venule or an arteriole surrounded by its perivascular space containing aqueous humor. However, recent microanatomic studies by Ashton [18] and by Thomassen and Bakken [19] have proved beyond doubt that biomicroscopically visible aqueous veins can be traced to their origin from Schlemm's canal.

Weekers and associates [20] objected to the accepted interpretation of the aqueous veins on the ground of their observations on rabbit eyes, which, after diathermic coagulation of all superficially visible blood vessels, showed only a short and insignificant increase in intraocular pressure. The fact that in Weekers' experiments afferent arteries, as well as the veins, were destroyed diminishes the convincing power of this argument.

Trantas [21] deduced from the occurrence of stratification in vessels far from the corneal limbus that "laminary veins" are not related to the elimination of aqueous fluid. Long ago [5a] it was pointed out that simultaneous visibility of aqueous humor and blood coursing through the same vessel is a unique occurrence, confined to the conjunctiva and episclera, while there are, in vertebrate physiology, analogies of stratification in vessels far remote from the eye and not at all connected with elimination of intraocular fluid.

Sugar [22] felt that the term "aqueous veins" might perhaps better be "plasma veins" because he was convinced that the canal contains "plasma plus that portion of aqueous which has entered the canal." He also stated the opinion that too much fluid is carried by the aqueous veins per minute to be compatible with the physiologic maintenance of intraocular pressure if their contents were entirely aqueous. The latter objection was also raised by Kleinert,[11b] who believed that some of the clear vessels surrounding the corneal limbus might be unconnected with the canal of Schlemm and might originate from the corneal tissue; a more probable explanation seems to be the generally accepted belief that smaller blood vessels all over the body may contain very few, or occasionally no, red blood cells.[5a] Sugar's first objection, the assumed plasma content of the canal, is built on a single histologic observation by Friedenwald, still awaiting confirmation. Even if the canal of Schlemm is fed by afferent arterioles, its main function seems to be the elimination of intraocular fluid, which, according to Friedenwald's assumption, is greatly aided by the addition of plasma to the contents of Schlemm's canal. General physiology knows of numerous regions where blood vessels contain blood deprived of most or all blood cells; such vessels may be called plasma vessels. The aqueous veins, however, even if containing some plasma, merit their distinctive denomination descriptive of their unique function of intraocular-fluid elimination.

17. Henderson, T., in discussion on Ascher,[8c] pp. 686-687.

18. Ashton, N.: Anatomical Study of Schlemm's Canal and Aqueous Veins by Means of Neoprene Casts: I. Aqueous Veins, Brit. J. Ophth. **35**:291-303, 1951; II. Aqueous Veins (continued), ibid. **36**:265-267, 1952.

19. Thomassen, T. L., and Bakken, K.: Anatomical Investigations into the Exit Canals of Aqueous Humor: A Preliminary Report, Acta ophth. **29**:257-268, 1951.

20. Weekers, R.; Heintz, A., and Prijot, E.: Recherches expérimentales sur les fonctions des veines aqueuses, Bull. Soc. belge opht. **94**:1-16, 1950.

21. Trantas, N.: Sur la nature des veines aqueuses d'Ascher, Acta XVI Conc. Ophth. London **1**:691-701, 1950.

22. Sugar, H. S.: The Glaucomas, C. V. Mosby Company, St. Louis, 1951, pp. 73-74.

As yet no investigator has succeeded in identifying the chemical constituents of the contents of an aqueous vein, but a number of facts prove the assumption that the aqueous veins are directly or indirectly connected with the canal of Schlemm and that they contain aqueous humor.

### PROOF OF CONTENTS OF AQUEOUS VEINS

1. Microanatomic and biomicroscopic investigations are in good agreement as to the continuity of the canal outlets with the aqueous veins, whereby the widest outlets from the canal of Schlemm correspond to the commonest location of the aqueous veins, as shown most convincingly in Theobald's,[23] Ashton's,[18] and Thomassen and Bakken's [19] specimens. The last two studies were undertaken for the express purpose of demonstrating the origin of aqueous veins previously identified intra vitam.

2. Pressure exerted upon the eye far from any aqueous vein produces an increase of the clear-fluid content of the aqueous veins and of their recipient vessels.[24] Trantas [21] doubted the conclusiveness of these experiments because the depth of the anterior chamber remained unchanged while compression was exerted. It is not probable, however, that the small amounts of additional fluid eliminated would produce an appreciable change in the depth of the chamber; besides, production of intraocular fluid would go on during this experiment to compensate for at least a part of the fluid expressed. Recent study of the resistance to outflow under tonometric pressure confirms this assumption.

3. Aqueous veins disappear in extremely hypotonic eyes after iridencleisis.[25] It is possible, however, that they have become so clear as to be indiscernible.

4. Dyes introduced into the anterior chamber appear in previously located aqueous veins, regardless of whether administered by instillation on the abraded corneal surface [26] or by injection into the chamber.[27]

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23. Theobald, G. D.: Schlemm's Canal: Its Anastomoses and Anatomic Relations, Tr. Am. Ophth. Soc. **32**:574-595, 1934.

24. (*a*) Ascher,[5a] p. 1197. (*b*) de Vries.[11a] (*c*) Goldmann, H.: Studien über den Abflussdruck des Kammerwassers beim Menschen, Ophthalmologica **114**:81-94, 1947. (*d*) Huggert, A.: Use of Privine as a Pressure-Reducing Medium in Iridocyclitis Glaucomatosa, Acta ophth. **28**:393-407, 1950. (*e*) Kleinert, H. W.: The Compensation Maximum: A New Glaucoma Sign in Aqueous Veins, A. M. A. Arch. Ophth. **46**:618-624, 1951.

25. (*a*) François, J.: Contribution à l'étude des veines aqueuses après l'iridencléisis, Ann. ocul. **182**:169-176, 1949. (*b*) Weekers, L., and Weekers, R.: Les fondements physiopathologiques et la technique de l'iridencléisis, Ophthalmologica **117**:305-324, 1949.

26. Huggert, A.: A Further Support to the Hypothesis That Ascher's Aqueous Veins Contain Aqueous Humor, Acta ophth. **27**:119-123, 1949.

27. (*a*) Goldmann, H.: Weitere Mitteilung über den Abfluss des Kammerwassers beim Menschen, Ophthalmologica **112**:344-349, 1946. (*b*) Busacca, A.: Personal communication to the author, Nov. 14, 1948. (*c*) Thomassen, T. L.: The Safety Valve of the Eye, Acta ophth. **27**:413-422, 1949. (*d*) Schulte, D.: Erfahrungen bei der Beobachtung von Wasservenen, Ber. Versamml. deutsch. ophth. Gesellsch. (1948) **54**:342-345, 1949. (*e*) Thomassen, T. L.: On the Exit of Aqueous Humor in Normal Eyes, Acta ophth. **28**:479-487, 1950. (*f*) Weekers, R., and Prijot, E.: Recherches expérimentales sur les fonctions des veines aqueuses, Ophthalmologica **119**:321-335, 1950.

5. Dyes injected intravenously or entering the blood vessels after oral administration are seen circulating in the conjunctival and episcleral blood vessels but do not appear in aqueous veins so long as they have not entered the anterior chamber [28]

6. During gonioscopic observation blood is seen leaving the canal of Schlemm at definite locations, which correspond to the sites of superficially visible aqueous veins of large diameter.[29] Trantas [21] was unable to see, gonioscopically, the outlets of Schlemm's canal, but Weinstein and Forgács [30] observed retrograde filling of the aqueous veins and the canal during compression of the jugular vein and simultaneous compression of the eyeball.

Embryologically, anatomically, and physiologically, the canal of Schlemm, the scleral meshwork, and the aqueous veins form a biologic unit charged with the elimination of intraocular fluid.

## FACTORS INFLUENCING THE CONTENTS OF AQUEOUS VEINS

Heart action, respiration, and illumination have a characteristic bearing on the contents of the aqueous veins.[5a] The pressure inside the aqueous veins is influenced by changes in position of the body.[9d] Illumination increases the elimination of fluid in many aqueous veins [5a] but may have the opposite effect if producing photophobia and blinking [31]; pressure of the lids hampers the flow in practically every aqueous vein.[32] Contact lenses may interfere with the elimination of intraocular fluid.[33]

Ethylmorphine hydrochloride, butacaine, and homatropine increase the amount of blood in the aqueous veins and in their recipient vessels,[34] while physostigmine, pilocarpine, glaucosan (an epinephrine-histamine preparation), and naphazoline (privine®) increase the output of clear fluid.[35] Epinephrine clears and contracts aqueous veins.[36]

## AQUEOUS VEINS IN GLAUCOMATOUS EYES

The detection of the aqueous veins, in May, 1941,[3] confirmed Leber's theory of a through-and-through circulation of intraocular fluid. With a continuous flow of aqueous humor leaving the canal through the aqueous veins, a continuous production of aqueous humor was postulated.[3] Having recognized the physiologic importance of the aqueous veins, I proceeded to consider their possible role in glaucoma.[37]

Aqueous veins occur in glaucomatous eyes also. In these eyes the qualities of aqueous veins differ somewhat from those of aqueous veins in eyes with normal

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28. Goldmann.[27a] Löhlein, H.: Über den Abfluss des Kammerwassers, Ber. Versamml. deutsch. ophth. Gesellsch. (1948) **54**:43-47, 1949.

29. van Beuningen, E. G. A.: Goniodynamometrie, eine Funktionsprobe im Kammerwinkel. Ber. Versamml. deutsch. ophth. Gesellsch. (1949) **55**:164-167, 1950.

30. Weinstein, P., and Forgács, J.: Conjunctival Angioscopy, Brit. J. Ophth. **35**:479-483, 1951.

31. Thomassen, T. L.; Perkins, E. S., and Dobree, J. H.: Aqueous Veins in Glaucomatous Eyes, Brit. J. Ophth. **34**:221-227, 1950.

32. Ascher.[5a] de Vries.[11a]

33. (*a*) Ascher.[8c] (*b*) Huggert, A.: Increase of Intraocular-Pressure When Using Contact Glasses, Acta ophth. **29**:474-481, 1951.

34. Ascher, K. W.: Aqueous Veins: Local Pharmacologic Effects on Aqueous Veins; Glaucoma and Aqueous Veins, Am. J. Ophth. **25**:1301-1315, 1942.

35. Ascher.[34] Gartner.[14a] de Vries.[11a] Huggert.[24d]

36. Ascher.[34] Weekers and Prijot.[8d] Wegner and Intlekofer.[8e]

37. Ascher,[3] p. 32.

pressure.[38] Further study is needed to confirm or to refute my impression that aqueous veins are less frequent in eyes with chronic simple glaucoma, that they are, on the average, smaller in glaucomatous eyes, and that their current is less vigorous. It is more difficult to find aqueous veins in eyes with congestive glaucoma and in eyes with secondary glaucoma due to iridocyclitis.[39] They are very rare in hydrophthalmos and in buphthalmos.[40]

It is not the congestion alone which makes the recognition of aqueous veins in glaucomatous eyes more difficult.[38] They reappear when the ocular pressure has been normalized by either miotics or surgery.[41] They disappear in extremely hypotonic eyes after iridencleisis or cyclodialysis [42]; it is a question, however, whether in these cases they have become so clear as to be indiscernible.

Aqueous veins of glaucomatous eyes may show an increased blood content as a premonitory sign of imminent pressure increase.[43] Intravascular pressure in aqueous veins of glaucomatous eyes seems to be lower than in aqueous veins of normal-pressure eyes [9d-f]; diurnal oscillations seem to be present, at least in some glaucomatous eyes.[21] One should not forget, however, that in normal-pressure eyes as well one may observe frequent and marked, apparently spontaneous, variations in aqueous veins.[44]

In glaucomatous eyes also an increase in clear fluid will [38a] appear in the aqueous veins after instillation of pilocarpine. This important fact was photographically recorded by Gartner [14a] and by Thomassen and associates.[31]

Sufficient evidence has accumulated since 1941 to prove the presence of a minutely balanced and changeable pressure differential between the two fluids, aqueous humor and blood, flowing in the recipient vessel of an aqueous vein.[5] When, by means of a small cotton applicator, a recipient vessel is compressed distal to the emptying of an aqueous vein, either expulsion of all blood from the blocked section of the vessel or filling with red blood cells may be observed.[5a] When compression is released, the picture reappears as it was prior to either phenomenon. These reactions, the aqueous-influx phenomenon and the blood-influx phenomenon, are apparently due to pressure differences in the sources from which the two fluids, blood and aqueous humor, derive, namely, the deep venous meshwork of the sclera and the canal of Schlemm. Neither the aqueous-influx phenomenon nor the blood-influx phenomenon represents an incidental or a transient quality; whenever the test is repeated, the same response is found, even after months and years, and is characteristic of the particular vessel.[38b] De Vries was the first to make photographic records of the blood-influx phenomenon.[11a]

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38. (*a*) Ascher, K. W.: Aqueous Veins: Local Pharmacologic Effects on Aqueous Veins; Glaucoma and Aqueous Veins, Am. J. Ophth. **25**:1301-1315, 1942; (*b*) Backflow Phenomena in Aqueous Veins of Normal and of Glaucomatous Eyes, ibid. **27**:1074-1089, 1944; (*c*) footnote 6.

39. Ascher.[38a] Huggert.[24d]

40. (*a*) Busacca, A.: Examen gonioscopique d'un cas d'hydrophtalmie, Ann. ocul. **181**:627-628, 1948. (*b*) Weekers, L., and Weekers, R.: Contribution à la pathogénie du buphtalmos, Ophthalmologica **120**:285-298, 1950. (*c*) Weinstein, P.: New Concepts Regarding Anterior Drainage of the Eye, Brit. J. Ophth. **34**:161-168, 1950.

41. Ascher.[38a] Thomassen and others.[31] François.[25a]

42. François.[28a] Weekers and Weekers.[25b] Goldmann, H.: Über die Wirkungsweise der Cyclodialyse, Ophthalmologica **121**:94-100, 1951.

43. Ascher.[38a,b] Thomassen.[27c] Thomassen and others.[31]

44. Ascher, footnotes 5a and 6.

One might expect that the high pressure prevailing in the anterior chamber of the glaucomatous eye would be transmitted to the canal of Schlemm, and thence into its invisible outlets, as well as into the visible aqueous veins; that therefore the aqueous outflow might be more vigorous in glaucomatous eyes, and that thus the aqueous-influx phenomenon might occur in glaucomatous eyes oftener than in eyes with normal pressure. This is not so; the compression of the recipient vessel in glaucomatous eyes is almost always followed by blood influx, whereby the venous blood streams in a direction opposite its normal flow, that is, not from, but back toward, the limbus.

Pressure applied to the eyeball externally, and far from any visible aqueous vein, may increase the clear stream in aqueous veins and in recipient vessels. This effect of increase in pressure, which I observed prior to 1942,[5a] was carefully studied by Goldmann [24c] in Berne, and by de Vries, in Amsterdam, in 1946.[11a] Using the spring balance, Goldmann measured the amount of external pressure which was needed to widen the diameter of the clear stream in a recipient vessel. For eyes with normal pressure both high and low increments of pressure were found, whereas for glaucomatous eyes only high readings were present so long as the ocular pressure was elevated. The real outflow pressure was measured by Löhlein [9b,f] by determining the difference between the intraocular pressure and the pressure in recipient vessels of aqueous veins. The average value for outflow pressure in normal eyes was 4.2 mm. Hg, but in glaucomatous eyes it was 13.1 mm. Hg.

According to Maggiore [45] and Theobald,[23] there are between 20 and 30 canal outlets in every human eye; the smallest outlets have diameters measuring 5 by 30 $\mu$; the diameters of the largest outlets, however, are 50 by 165 $\mu$. It is reasonable to assume that an outlet with a cross-sectional area 60 times as large as a small cross-sectional area will be more effective for elimination of fluid. In some eyes, only a few large outlets may carry the main bulk of the intraocular fluid; occasionally, it may be even only one large outlet. In eyes of this type, occlusion of a few, or even one, outlet may result in pronounced increase in intraocular pressure.[5a,b,e]

### ROLE OF AQUEOUS VEINS IN RETENTION THEORY OF GLAUCOMA

In June, 1941, a few weeks after the detection of the aqueous veins, I wrote to Derrick Vail, then head of the department of ophthalmology of the University of Cincinnati College of Medicine, that I was anxious to study the characteristics of aqueous veins in glaucomatous eyes. By the end of the year 1941 I was convinced that "the main difference between aqueous veins in normal eyes and in those with primary compensated glaucoma seems to be that in the latter the glass-rod phenomenon is apparently extremely rare." In eyes with normal pressure, both the aqueous-influx and the blood-influx phenomenon can be observed and are characteristic of the individual aqueous veins.[46] By that time I understood that "in glaucomatous eyes with normal venous pressure in the conjunctival veins, a steeper pressure gradient and a more vigorous glass-rod phenomenon should be expected." [47] Thinking along similar lines, Verhoeff asked, when discussing my presentation

45. Maggiore, L.: Struttura, comportamento e significato del canale di Schlemm nell'occhio umano in condizione normali e patologiche, Ann. ottal. e clin. ocul. **40**:317-462, 1917.

46. Ascher,[38a] p. 1314.

47. Ascher,[38a] p. 1311.

before the Association for Research in Ophthalmology, in 1942, whether with "a normal filtration angle and high intraocular pressure the aqueous flow would be increased and the clear stream [in aqueous veins] would be longer." [48]

In a first attempt to explain the rare occurrence in glaucomatous eyes of the aqueous influx during compression of the recipient vessel of an aqueous vein, I referred to a study by Colomba,[49] who, in 1938, claimed that the average venous systemic pressure of glaucomatous persons was higher than that of persons with normal intraocular pressure. This assumption was later confirmed, to a certain degree, by Thomassen [50] and by Duke-Elder,[51] who found in glaucomatous eyes an aqueous-influx phenomenon during the phase of decreasing ocular pressure which coincided with a fall in the pressure of the episcleral veins while during the diurnal phase of ascending ocular pressure the aqueous-influx phenomenon was absent and the pressure in the episcleral veins increased. De Vries [11a] had found that the aqueous-influx phenomenon occurs in aqueous veins with rapidly streaming contents, and the blood-influx phenomenon, in aqueous veins with slow current.

There seemed to be a good correlation between dynamic changes in the influx phenomena during compression of the recipient vessels and the functional fluctuations in venous pressure, whether local or systemic.[52] This neurovascular approach, however, could not explain certain discrepancies between biomicroscopical and gonioscopic observations. When the canal of Schlemm and the aqueous veins are considered as a physiologic unit, the phenomena observed in the aqueous veins are to be correlated with those occurring in the canal during gonioscopic observation. While blood can easily be found in the canal of eyes with normal pressure during gonioscopy, it rarely appears in the canal of glaucomatous eyes,[53] even if every effort is made to force it into the canal.[54] During compression of the recipient vessel, however, blood is seen streaming backward to the limbus in all cases in which the aqueous-influx phenomenon is absent and blood would be expected to enter the canal. Only during the phase of falling pressure in glaucomatous eyes did Thomassen [50] and Duke-Elder [51] observe aqueous-influx phenomena; these occur also in the aqueous veins occasionally encountered in corneal scars of glaucomatous eyes.[55] Otherwise all observers agree that the blood-influx phenomenon is the rule

48. Verhoeff, F. H., discussion on Ascher,[38a] p. 1314.

49. Colomba, N.: Clinical Researches on the Venous System of Glaucomatous Patients. Lettura oft. **15**:323-339, 1938; abstracted, Am. J. Ophth. **25**:359, 1942.

50. Thomassen, T. L.: The Glass-Rod Test in Glaucomatous Eyes, Brit. J. Ophth. **33**:773-778, 1949.

51. Duke-Elder, W. S.: The Dependence of Surgery on Physiology, with Special Reference to the Treatment of Glaucoma, Am. J. Ophth. **33**:11-18, 1950.

52. Ascher.[38a] Colomba.[49]

53. Kronfeld, P. C.; McGarry, H. I., and Smith, H. E.: Gonioscopic Studies on the Canal of Schlemm, Am. J. Ophth. **25**:1163-1173, 1942.

54. Hobbs, H. E.: The Trabecula in Chronic Simple Glaucoma, with Special Reference to the Gonioscopic Appearance of Blood in the Canal of Schlemm, Brit. J. Ophth. **34**:489-494, 1950.

55. Wegner and Intlekofer.[8c] Kleinert.[11b] Weekers, R., and Delmarcelle, Y.: Veines aqueuses et veines laminaires néoformées dans un leucome cornéen, Acta ophth. **29**:85-89, 1951. Löhlein, H.: Beobachtungen an einer Hornhautkammerwasservene und die Frage ihrer Entstehung, Klin. Monatsbl. Augenh. **119**:618-628, 1951. Trantas, N.: Veines laminaires dans la cornée sur un case de leucome du à une brûlure, Bull. Soc. hellénique d'opht. **18**:59, 1951.

in glaucomatous eyes. The obvious discrepancy—backflow of blood toward the canal, but not into it, in glaucomatous eyes and either blood backflow, with filling of the canal, or aqueous-influx phenomenon, with emptying of the canal, in eyes with normal pressure—led me, in 1943, to the assumption of a possible narrowing of the canal outlets of glaucomatous eyes, a hypothesis which I published in 1944.[38b] This hypothesis also proved to be helpful in the elucidation of a great number of since-accumulated observations on glaucomatous eyes.

Mathematical evaluation [56] proved that among the factors responsible for drainage of aqueous humor from the canal, the number of outlets, their width, and the eccentricity of their cross section are most important. In Poiseuille's equation, the radius of the tube occurs at the fourth power, indicating that narrowing of an outlet will markedly increase the resistance to the outflow.[56]

Histologic confirmation of this hypothesis of a narrowing of canal outlets is not yet available, but Focosi,[57] in 1948, found calcareous obstruction of one canal outlet in the eye of a patient who died eight days after his first, easily controlled glaucomatous attack.[58]

In normal-pressure eyes, external experimental pressure increases with ease the amount of clear fluid eliminated through the aqueous veins [24a,e]; the opposite is observed in glaucomatous eyes, whether compression is exerted on the cornea, on the sclera, or through the lids.[59] In normal-pressure eyes, the clear stream in the recipient vessel may be broadened by slight, medium, or heavy pressure of the dynamometer, according to the width of the aqueous vein observed; in glaucomatous eyes, widening of the aqueous thread occurs only at higher values of external pressure. In Kleinert's compensation-maximum test a measurable compression of the eyeball is followed in eyes with normal pressure by broadening of the clear stream in aqueous veins, whereas the same, or even lower, pressures produce backflow of blood into the aqueous veins of glaucomatous eyes.[59a,d]

While expecting that these observations might be evolved into a clinically useful glaucoma test on aqueous veins, Kleinert did not fail to mention that in some normal eyes relatively low pressure may force blood into the aqueous veins as well; this observation was confirmed in a recent study performed in the University of Cincinnati department of ophthalmology.[59a] These different responses of eyes with normal pressure to the compensation-maximum test are in accord with the different responses of aqueous veins in normal-pressure eyes to the compression test of the recipient vessels [5] and also with the different values of resistance to outflow.[60] While

56. Ascher, K. W., and Spurgeon, W. M.: Compression Tests on Aqueous Veins of Glaucomatous Eyes: Application of Hydrodynamic Principles to the Problem of Intraocular-Fluid Elimination, Am. J. Ophth. **32**:239-251 (June, Pt. 2) 1949.

57. Focosi, M.: Osservazioni istologiche su di un caso recente di glaucoma acuto, Boll. ocul. **27**:209-227, 1948.

58. Search for possible absence or narrowness of canal outlets or an unusually low number of them, is desirable in cases of congenital glaucoma; in secondary glaucoma, disease of the cornea, sclera, or ciliary body might interfere demonstrably with the patency of these outlets; in primary glaucoma, sclerosing of the outlets might be expected, since their anatomic structure so clearly resembles that of small intrascleral vessels,[19] a process analogous to the vascular changes observed in other regions of the glaucomatous eye.

59. (*a*) Ascher, K. W.: Unpublished data. (*b*) Goldmann.[24c] (*c*) Huggert.[24d] (*d*) Kleinert.[24e]

60. Grant, W. M.: Clinical Measurements of Aqueous Outflow, A. M. A. Arch. Ophth. **46**:113-131, 1951.

normal-pressure eyes usually show a free aqueous outflow when subjected to continuous tonometric pressure, most glaucomatous eyes and a certain percentage of normal-pressure eyes give unusually high readings.[61]

## CONCLUSIONS

It seems, therefore, that the following show a close relation: resistance to outflow, as evaluated by continuous tonometric pressure; response to the compensation-maximum test; response to compression of the cornea with a dynamometer; the compression test performed on the recipient vessel; the rate of flow of aqueous humor as observed biomicroscopically, and the gonioscopic appearance of blood in the canal of Schlemm. One group of responses occurs in both the normal-pressure and the glaucomatous eye; the other type is characteristic of the normal-pressure eye, without being its sole response. In the same normal-pressure eye, aqueous veins may present responses consistent in the individual vessel, but varying from vessel to vessel; the same is true of the response to dynamometric pressure and to the compensation-maximum test. In glaucoma, as everywhere, we must not expect sharp dividing lines between the normal and the pathologic; seeming exceptions, which initially confuse the observer, may help to elucidate intricate pathophysiologic problems. Histologically, in normal eyes both wide and narrow canal outlets are found; therefore, either the aqueous- or the blood-influx phenomenon may be observed, but one of them consistently in the individual aqueous vein; during the increment-of-pressure test low or high dynamometric readings are found, according to whether the observed aqueous vein derives from a wide or a narrow outlet; the canal may or may not show backflow of blood, depending on the width of its outlets; compensation-maximum readings are mostly high, but sometimes low, the latter being probable if an aqueous vein from a narrow outlet is being studied; resistance to outflow is mostly low, but sometimes high, the latter being most likely if many of the outlets are narrow.

The hypothesis of a narrowing of the outlets of Schlemm's canal would easily explain the rare occurrence of aqueous veins in certain types of glaucoma. It would account for the fact that in glaucomatous eyes the clear-fluid stream in aqueous veins is not longer, wider, faster, or more vigorous than in aqueous veins of eyes with normal intraocular pressure; that in glaucomatous eyes compression of the recipient vessel rarely evokes the aqueous-influx phenomenon; that after the compression test stratification reappears slowly [40c]; that blood streaming toward the limbus during the compression of the recipient vessel of a glaucomatous eye rarely becomes visible inside the canal; that in eyes with glaucoma controlled by miotics or by surgery the aqueous-influx may be observed; that in glaucomatous eyes more pressure must be applied to the bulbus in order to increase the visible flow of aqueous humor; that relatively low dynamometric pressure may force blood into the aqueous veins of glaucomatous eyes during the compression-maximum test, and that the resistance to outflow, calculated from continuous tonometric pressure,[60] is higher in glaucomatous eyes than in normal-pressure eyes.

The responses found in glaucomatous eyes seem to be more characteristic of narrowness of the canal outlets than of the glaucoma itself; they occur in normal-pressure eyes as well. If, however, many outlets of an eye react as mentioned above,

61. de Roetth, A., Jr., in discussion on Grant.[60]

increase in intraocular pressure is likely to ensue. At least in the beginning, these constrictions of the canal outlets should be assumed to be of a transient, functional type the pathogenesis of which is, of course, open to speculation, as is also the more permanent narrowing which follows (Table).

It is obvious that all these facts seem to support the retention theory of glaucoma and that, according to the considerations previously mentioned, the obstacle to flow—whether permanent or transient—should be suspected to be in the canal outlets. Theoretically, other locations of the obstacle might be the trabeculum, the canal, the aqueous veins, or their recipient vessels, obstacles in the last two possible sites being of the functional type and those of the first, of anatomic nature. The

*Effect of Width of Canal Outlets and Aqueous Veins*

| Effect on | Wide Outlets | Narrow Outlets |
|---|---|---|
| **Gonioscopic findings** | | |
| Backflow of blood into the canal of Schlemm | Frequent | Rare |
| **Biomicroscopic findings** | | |
| (*a*) Rate of flow of aqueous humor, observed on recipient vessel | High | Low |
| (*b*) Compression test, performed on recipient vessel, observed on aqueous vein: influx phenomenon | Aqueous influx | Blood influx |
| (*c*) Reappearance of stratification after compression test (Weinstein) | Quick | Slow |
| (*d*) Increment pressure test, performed on cornea, observed on recipient vessel: dynamometric readings | Low | High |
| (*e*) Pulsations in aqueous veins (Kleinert) | Frequent | Rare |
| (*f*) Compensation-maximum test (Kleinert) | Even dynamometer pressure of 150 gm. does not force blood into the aqueous veins (normal-pressure eyes only) | Dynamometer pressure readily forces blood into aqueous veins (one-third of normal-pressure eyes; most glaucomatous eyes) |
| Outflow-resistance test (Grant, de Roetth) | Low resistance; tonometer produces deep indentation (normal-pressure eyes only) | High resistance; tonometer produces shallow indentation (some normal-pressure eyes; most glaucomatous eyes) |
| Intraocular pressure<br>Tonometric readings | Normal if no other pathology | High if many outlets are narrow |

considerations outlined above, however, favor the transient or permanent narrowing of the canal outlets as the most logical and most comprehensive explanation of all phenomena observed, and therefore as a tentative hypothesis for the pathogenesis of at least some types of glaucoma.

Two groups of experiments on aqueous veins have given support to the retention theory of glaucoma, without excluding the neurovascular explanation: 1. Schmerl [8n] and Weekers and Prijot [8d] found, after instillation of hydroxyamphetamine (paredrine®) and epinephrine, respectively, definite constriction of aqueous veins of rabbit eyes, followed by increase in intraocular pressure. 2. Huggert [33b] observed increase in intraocular pressure in 25 of 33 eyes wearing contact lenses with narrow haptic for 30 minutes; in 9 of these eyes the increase in intraocular pressure amounted to 10 mm. Hg or more. Interference of contact lenses

with aqueous veins has been described previously [8c]; it was found that aqueous outflow may be blocked, or at least retarded, by contact lenses even if they rest gently on the conjunctival surface.

## SUMMARY

It is not implied that the narrowing of canal outlets alone supplies the mechanism for elevation of intraocular pressure to abnormal values in all cases of glaucoma, and certainly not without subsequent development of characteristic anatomic changes. However, narrowing or obstruction of canal outlets may be accorded primacy in some cases of glaucoma.[62]

I fully realize that my report is fragmentary and incomplete, as is all the work which has been done in this new field of research. It will take many years of continued effort and pooling of data by all interested in this problem before the aspects and potentialities of the aqueous veins will have been thoroughly explored. The methods to be used should include physiologic, biochemical, pharmacologic, and clinical procedures. Histologic verification should be supplied for the working hypothesis that a narrowing of the canal outlets seems to be connected with, or even may become responsible for, the increase in pressure in at least some eyes with primary simple wide-angle glaucoma. This factor may as yet be purely hypothetic, but it is possible that it plays an important part in setting the scene for the tragedy of glaucoma. As time goes on, one may expect that the aqueous veins will become a source of further light on the problems of physiology and pathology of the intraocular pressure.

## ABSTRACT OF DISCUSSION

DR. HAROLD G. SCHEIE, Philadelphia: I very much appreciate the opportunity of discussing Dr. Ascher's paper, because I have admired his work so greatly. Without doubt, he has described a new anatomicoclinical entity, a feat which is not easy at this stage of medical development. I am in complete agreement with his statements regarding it.

The first suggestion that aqueous veins might exist probably could be derived from Troncoso's work, in which he obtained specimens of blood from the anterior segment of the eye at the limbus and found that, as compared with blood elsewhere in the body, it was considerably diluted. He calculated aqueous flow on that basis.

The next suggestion of veins leading from the canal of Schlemm was presented by Theobald, who showed by beautiful anatomic studies that venous channels arose from the canal. Ascher later demonstrated vessels containing watery fluid in the conjunctiva and superficial sclera. However, it remained for Ashton, by neoprene casts, during the past year and a half, and for Thomassen and Bakken to prove that these vessels did actually connect with the canal of Schlemm.

As with any new entity, there is considerable discussion about the significance of these vessels. We can be fairly certain now, as a result of Ascher's work, and later of Ashton's work and that of many others, that these vessels play a vital part in carrying aqueous away from the anterior chamber of the eye. It is very possible that they may play an important role in glaucoma, for it seems likely that the elevated intraocular pressure of glaucoma results from disturbances in outflow of aqueous. This concept has been widely accepted in the United States as a result of concepts which have arisen from extensive gonioscopic studies and from the very beautiful and precise studies of Grant by tonographic methods. Obstruction may occur in the angle at any of several locations. The trabeculum might be involved,

62. Ascher, K. W.: Aqueous Veins and Their Significance for Pathogenesis of Glaucoma, Arch. Ophth. **42**:66-76, 1949; footnotes 6 and 38b.

as has been suggested in pigmentary glaucoma. There are undoubtedly many other types, such as the cuticular membrane found by Reese to cover the trabeculum.

Other possible sites of obstruction might be the canal of Schlemm itself or, as a result of Ascher's work, the aqueous veins. Ascher has suggested that the openings of the aqueous veins in the canal of Schlemm may be narrowed. Changes in the aqueous veins themselves farther from the canal, even as far as the surface of the globe, must be considered. As yet, however, the evidence in favor of aqueous veins as an etiologic factor in wide-angle glaucoma is entirely theoretical, no positive proof having been obtained. Kronfeld's studies regarding the filling of the canal of Schlemm with blood are probably the best evidence so far. He found that blood regurgitated with greater difficulty into the canal of Schlemm in eyes with chronic simple glaucoma than in normal eyes.

Since we are still searching for the cause or causes of chronic simple glaucoma, we are grateful to Dr. Ascher for having opened at least one more pathway that must be followed in our research into that disease. His work should be given even more recognition than it has received, and he certainly deserves all the praise he has received.

DR. K. W. ASCHER, Cincinnati: I want to thank Dr. Scheie for his discussion. He was one of the first, with Derrick Vail, Frederick Verhoeff, Uribe Troncoso, Lawrence Post, and Duke-Elder, who 10 years ago did not smile too much when I mentioned the aqueous veins.

In my first 1942 report on the aqueous veins I gave credit to Uribe Troncoso for proving the exit of intraocular fluid in animal experiments, and to Dvorak-Theobald for showing these pathways in the human eye. I claimed only the biomicroscopic detection of these pathways. However, I want to mention, as I have before, that Andrew deRoetth, now in Spokane, while a resident in the University Eye Clinic of Debrecen, Hungary, some 25 years ago, showed an aqueous vein to his professor, who said, "Oh, forget about it; it doesn't mean much." Thus, deRoetth may have been the first to recognize an aqueous vein as such, without persuing his observation.

(Slide) This slide gives the answer to the question of the obstruction of the trabeculum, which was thought by some to be responsible for increase in intraocular pressure. If one assumes that a thickening or hardening of the trabeculum is responsible, then, upon compression of the recipient vessel, blood should be forced into the canal of Schlemm as easily as it is in normal-pressure eyes. With the obstacle located between the anterior chamber and the canal, the pressure inside the canal would be low, and there would be no reason that blood should not be permitted to enter the canal. The discrepancy between the easy entrance of blood into the canal of normal-pressure eyes and the difficulty in forcing it into the canal of glaucomatous eyes was my main point in assuming a possible narrowing or obstruction of the canal outlets. This hypothesis would explain why in glaucomatous eyes blood would stream toward, but not into, the canal of Schlemm during compression of the recipient vessel. Histologic work should follow along the same lines as that by Theobald and by Ashton, to verify or to refute these assumptions.

# Annual Reviews

## LENS AND VITREOUS

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DURING the past year a number of notable articles have been added to the literature of the lens and vitreous. Some progress has been made toward elucidation of the chemistry and metabolism of the lens. The work on irradiation of the lens has continued and shows promise of shedding light on the mechanism of cataract formation. Unfortunately, it has been impossible to include all the many interesting papers on the lens and vitreous, and therefore I have attempted to cover only those of major importance.

### THE LENS

STRUCTURE; DEVELOPMENT; CHEMISTRY; METABOLISM

*Structure; Development.*—Using the phase-contrast microscope, François and Rabaey [1] studied and photographed the in vivo lens epithelium. Two types of cells were observed in cataractous lenses. One type was a pale polyhedral cell with many well-defined granulations in the perinuclear area, which the author speculated might be concerned with enzymatic reactions. The other type was dark and star-shaped. The vacuolation which precedes opacification of the lens was well demonstrated with this type of microscope. Pirie [2] has found that the capsule of the ox lens is composed of a single protein very similar to collagen except for its high carbohydrate content.

In a study to determine the age changes in the lens of the Wistar albino rat, Leopold and Calkins [3] found that between the ages of 21 and 850 days the lens nearly doubled its spherical size and the anterior capsule nearly doubled its thickness. After the age of 100 days the outer layers of the anterior capsule showed a tendency to split and flake off.

*Chemistry and Metabolism.*—De Vincentiis and Auricchio [4] have studied the metabolism of the chick lens in embryonal and postnatal life. There was a rapid decrease in the respiratory activity from the 12th day of incubation to the time of birth. Glycolysis decreased slowly up to the 14th day. Both processes are more active during the first days of life than in the adult period. Pentini [5] states that

1. François, J., and Rabaey, M.: In Vivo Examination of the Lens by the Phase-Contrast Microscope, Brit. J. Ophth. **35**:352-355, 1951.

2. Pirie, A.: Composition of Ox Lens Capsule, Biochem. J. **48**:368-371, 1951.

3. Leopold, I. H., and Calkins, L.: Age Changes in the Wistar Albino Rat Eye, Am. J. Ophth. **34**:1735-1740, 1951.

4. de Vincentiis, M., and Auricchio, G.: Riserche sul ricambio della cornea e del cristallino durante la vita embrionale, ital. ottal. **2**:69-82, 1951; abstracted, Am. J. Ophth. **34**:1772, 1951.

5. Pentini, G.: L'occhio nella sindrome generale di adattamento: "Variazioni del consumo di $O_2$ del cristallino," Ann. ottal. e clin. ocul. **77**:254-263, 1951; abstracted, Am. J. Ophth. **34**: 1775-6, 1951.

in experiments on the oxygen uptake of the lens the addition of dextrose increases the uptake. The oxidation reaction is retarded in lenses from animals previously treated with corticotropin or desoxycorticosterone acetate.

Christiansen and Leinfelder [6] have recently made the claim that the oxygen uptake of isolated lenses is a nonliving, nonenzymatic chemical oxidation, and as such is of little significance in the physiology of the lens. They cite the following experimental data to support their contention: 1. No difference in the rate of oxygen uptake was observed in determinations on 116 fresh lenses and 76 boiled lenses. Boiling would certainly have destroyed all enzymatic activity. 2. Chemical denaturation of the surface proteins of the lens did not decrease the rate of oxygen uptake. 3. The relation of the pH to the rate of oxidation indicates that the reaction is strongly catalyzed by alkali, a process which is characteristic of a chemical oxidation. 4. The noncellular interior of the lens appeared to participate in the oxidation reaction to approximately the same extent as the epithelium and peripheral cortex.

In a study of the glycolysis of the lens the same authors [7] found that the capacity of the lens to convert dextrose to lactic acid is lost by boiling or otherwise denaturing the lens protein, so that glycolysis is a heat-labile enzymatic process. It is dependent upon dextrose as a substrate; glycogen is a less satisfactory substrate. The reaction appears to proceed independently of the oxygen tension. Anaerobic and aerobic glycolysis proceed at approximately the same rate. Experiments with partial boiling of the lens indicate that a substantial amount of glycolysis is carried out by the cortical material in the deeper layers of the lens.

Kinsey and Frohman [8] have reported on the distribution of cytochrome, riboflavin, lactate, and pyruvate in the epithelium, cortex, and nucleus of the lens. According to their results, both the flavoprotein and the cytochrome-oxidase systems are present in high concentrations in the epithelium, as compared with negligible concentrations in the remainder of the lens. The concentration of lactate is deficient in the epithelium, while that of pyruvate is high; exactly the reverse relation between the two occurs in the nucleus and the cortex. The deficiency of lactate in the epithelium indicates that the cytochrome oxidase there localized is acting, at least partially, in the metabolism of carbohydrates. It would thus appear that the epithelium is the site of a completely aerobic type of metabolism with a high oxygen uptake, as compared with that of other tissues, while the cortex and nucleus have a strictly anaerobic type of metabolism. The authors suggest that a vital function of the epithelium may be the providing of energy for the entire lens.

Ely [9] has also reported on the isolation and identification of cytochrome c in the animal eye. Using specimens consisting of pooled whole bovine lenses, he found the concentration of cytochrome c to be 2.53 γ per lens. Kinsey and Frohman [8]

6. Christiansen, G. S., and Leinfelder, P. J.: A Critical Study of Lens Metabolism: I. Nonenzymatic "Respiration," Am. J. Ophth. **35**:21-32, 1952.

7. Leinfelder, P. J., and Christiansen, G. S.: A Critical Study of Lens Metabolism: II. Glycolysis, Am. J. Ophth. **35**:33-38, 1952.

8. Kinsey, V. E., and Frohman, C. E.: Studies on the Crystalline Lens: Distribution of Cytochrome, Total Riboflavin, Lactate, and Pyruvate and Their Metabolic Significance, A. M. A. Arch. Ophth. **46**:536-541, 1951.

9. Ely, L. O.: The Cytochrome-C Content of Bovine Crystalline Lens, A. M. A. Arch. Ophth. **47**:717-719, 1952.

found the concentration to be 4.3 γ per epithelium-capsule portion of each bovine lens. Both results were obtained spectrophotometrically, but with different modifications.

In another study, Frohman and Kinsey [10] have determined the concentrations of specific compounds containing high-energy phosphate bonds in the various parts of the lens. The concentration of readily utilizable high-energy phosphate (adenosinediphosphate and adenosinetriphosphate) was highest in the epithelium-capsule portion. The concentration of these same substances in the nucleus was negligible, and the concentration in any portion of the cortex varied approximately inversely from the distance of that portion to the epithelium. The concentration of phosphocreatine in the lens (the storage form of high-energy phosphate) was highest in the posterior cortex and lowest in the epithelium. Inorganic phosphate was in highest concentrations and lowest in the nucleus and the posterior cortex. The concentration gradient of the adenosinephosphates is compatible with the theory that these compounds are produced in the epithelium through its oxidative metabolism and then diffuse posteriorly through the lens. It could also be accounted for by the diffusion of other energy-rich organic phosphate compounds, which would affect the rate of production of this compound through anaerobic glycosis. It would appear that the concentration gradient of adenosinephosphates is not without physiologic significance, since the concentrations of these energy-producing compounds in the various portions of the lens parallel the rate of protein synthesis.

Schmerl [11] calls attention to experiments which may have been previously overlooked and which demonstrate that normal animal lenses contain a substance capable of causing a bleaching action in lenses which are brown due to nuclear sclerosis.

### Congenital Anomalies

Holst [12] has investigated the statistics of blindness due to congenital cataract in Norway. In a group of 253 patients, he states that 193 could not see to read and 101 could not see to walk. Friedman and Wright [13] present a pedigree of hereditary microcornea and cataract comprising five generations, in which 8 of 37 members were affected. The defects were transmitted as dominant characteristics. The microcornea was not associated with microphthalmos. Visual results following surgical measures were generally good in all cases but one, in which glaucoma was a complication. Renard and Laporte [14] report a rare case of bilateral congenital cataract in an 8-year-old child, characterized by crystal formation in the axial region of the lens. This cataract, which occurred on a hereditary basis, was classified as coralliform. Kirman [15] describes a case of congenital familial bilateral cataract associated with imbecility (Langan intelligence quotient, 49). In three generations, four

10. Frohman, C. E., and Kinsey, V. E.: Studies on the Crystalline Lens: V. Distribution of Various Phosphate-Containing Compounds and Its Significance with Respect to Energetics, A. M. A. Arch. Ophth. **48**:12-18, 1952.

11. Schmerl, E.: Experimental Bleaching of Cataractous Lens Substance, Am. J. Ophth. **35**:1033, 1952.

12. Holst, J. C.: Occurrence of Blindness in Norway, Am. J. Ophth. **35**:1153-1166, 1952.

13. Friedman, M. W., and Wright, E. S.: Hereditary Microcornea and Cataract in 5 Generations, Am. J. Ophth. **35**:1017-1021, 1952.

14. Renard, G., and Laporte, P.: Les cataractes congénitales à cristaux, Arch. opht. **11**: 739-753, 1951.

15. Kirman, B. H.: Familial Cataract and Mental Deficiency, Lancet **1**:694-696, 1952.

persons were afflicted with cataract, a fifth with mental deficiency, and a sixth with epilepsy. In experiments in which thyroxine was fed to pregnant rats, Giroud and de Rothschild [16] found that congenital cataract resulted in the offspring in a large proportion of animals.

Ingalls, Tedeschi, and Helpern [17] report on a congenital anomaly of newborn mice known as "open eye." Although the syndrome is an occasional chance development, in the majority of the cases which they report it was the result of maternal anoxia during the last several days of the gestation period. In addition to calling attention to the similarity to retrolental fibroplasia of the retinal pathology in this condition, the authors describe an accompanying pathologic process in the lens and the vitreous. The vitreous was reduced in size and irregular in shape and contained large vacuoles. There was an abnormality of the retrolental vascular system. The lens was greatly distorted and displaced forward against the posterior surface of the cornea. The capsule appeared thickened and detached from the lens substance. The posterior portion of the lens included masses of degenerate-appearing cells and cellular debris.

Snyder [18] reports that of 74 women who were vaccinated for smallpox during pregnancy, no evidence of congenital cataract or other ocular pathology was found in the eyes of the offspring, indicating that the procedure is harmless from the point of view of the eye. It is probable that the variola virus is too large to pass through the placental barrier.

Töndury [19] examined the eyes of five embryos, all of whose mothers had rubella between the 21st and the 37th day of pregnancy. The eyes showed degeneration of the lens fibers, thickening of the capsule, and microphthalmos. In four embryos the cataract was central, and in one, peripheral.

### Cataracts Associated with Endocrine Disturbances

*Diabetes.*—In a consideration of the ocular changes in diabetes, Cordes [20] discusses the true diabetic cataract and the senile cataract in diabetes. He remarks that the use of insulin has favorably altered the previously poor surgical prognosis in these cataracts, so that postoperative bleeding is no longer a prominent complication, nor is postoperative infection. The true diabetic cataract requires a linear extraction in order that hemorrhage may be reduced to a minimum, and this should be combined with an iridectomy if good preoperative dilation of the pupil cannot be achieved. The visual prognosis depends mainly on the presence or absence of retinopathy. If only small hemorrhages are present, the outlook is good; but engorged veins, large retinal hemorrhages, vitreous hemorrhages, retinitis proliferans, and detachment are contraindications to surgery. In a group of 61 cases of

16. Giroud, A., and de Rothschild, B.: Cataracte congénitale après thyroxine, Bull. Soc. opht. France **5**:543-549, 1951; abstracted, Excerpta med. XII **6**:162, 1952.

17. Ingalls, T. H.; Tedeschi, C. G., and Helpern, M. M.: Congenital Malformations of the Eye Induced in Mice by Maternal Anoxia, with Particular Reference to the Problem of Retrolental Fibroplasia in Man, Am. J. Ophth. **35**:311-329, 1952.

18. Snyder, S. S.: Effect of Maternal Smallpox Vaccination During Pregnancy on the Eyes of the Infants, Am. J. Ophth. **34**:1713-1715, 1951.

19. Töndury, G.: Beitrag zur Kenntnis der Embryopathia rubeolosa und iherer Wirkung auf die Entwicklung des Auges, Klin. Monatsbl. Augenh. **119**:449-459, 1951.

20. Cordes, F. C.: The Diabetic: His Visual Prognosis, A. M. A. Arch. Ophth. **48**:531-556, 1952.

juvenile diabetes, Marr [21] found no instances of diabetic cataract. He expresses the opinion that careful regulation of the disease reduces the incidence of cataract and believes that his cases, which represent a group in which better than average control of the diabetes is maintained, lend weight to this impression.

In a series of 21 rats made diabetic with alloxan, Janes, Bounds and Leinfelder [22] confirm the observation of others that severe diabetes must be present for some time before cataract will develop. Two animals in their series, with blood sugar levels ranging from 140 to 160 mg. per 100 cc., failed to show lens opacification during 20 weeks of observation. In the remaining animals of the series four to eight weeks was required for the development of early cataractous changes and six months for complete opacification. It was noted that the addition of excess amounts of nicotinic acid to the diet caused some delay in the occurrence and progression of the cataracts. Kok-van Alphen [23] found that cataracts formed in animals with alloxan diabetes approximately four weeks after the injection. The intensity of the cataract was roughly proportional to the blood sugar level. Insulin prevented cataract formation if administered sufficiently early and controlled its progress, once formed.

Patterson,[24] in a study of alloxan- and dehydroascorbic-acid-produced diabetic cataracts in rats, reports on the relation of the severity of the diabetes to the time required for cataract formation. Using the complete opacification of the lens readily observed with the unaided eye as the end-point for determining the time interval, he found that in rats with high blood sugar levels cataract developed in both eyes in 8 to 10 weeks, and that in those with low blood sugar levels cataract developed more slowly, occasionally unilaterally, and usually at different times in the two eyes. The author states that a hyperbolic equation gives the best mathematical expression of the correlation between the data for the blood sugar level and the data for the time interval. The equation indicates that cataract should not appear before the week of the 40th day and should not occur with blood sugar levels of less than 225 mg. per 100 cc. In order to demonstrate that the cataracts he had produced were due to diabetes, and not to the diabetogenic factors employed, the author treated a series of rats with diabetes of two weeks' duration with daily injections of insulin sufficient to lower their blood sugar levels from between 400 and 600 mg. to below 250 mg. per 100 cc. Whereas control rats exhibited cataracts in approximately 10 weeks, the insulin-treated rats showed no evidence of cataract formation, as seen with the ophthalmoscope, over a period of six months. The author reiterates his hypothesis that diabetic cataract may result from the loss of an essential metabolite sharing a common reabsorption pathway with glucose, and he further suggests that diabetic and parathyroid cataract may result from a common metabolic deficiency.

*Dermatitis.*—Bentolila, Ortiz, and Bertotto [25] report a case of bilateral cataract associated with neurodermatitis of long duration. The opacities were located cen-

21. Marr, W. G.: Cataracts and Retinopathy in Juvenile Diabetics, Am. J. Ophth. **35**: 577-582, 1952.

22. Janes, R. G.; Bounds, G. W., and Leinfelder, P. J.: Ocular Complications in the Rat Made Diabetic with Alloxan, A. M. A. Arch. Ophth. **48**:414-419, 1952.

23. Kok-van Alphen, C. C.: Lensverandering bij alloxaandiabetes, Nederl. tijdschr. geneesk. **96**:59, 1952; abstracted, Excerpta med. XII **6**:364, 1952.

24. Patterson, J. W.: Development of Diabetic Cataracts, Am. J. Ophth. **35**:68-72 (May, Pt. 2) 1952.

25. Bentolila, L.; Ortiz, J. M. V., and Bertotto, E. V.: Allergic Cataract, Ann. Allergy **10**:36-37, 1952.

trally in the anterior cortex and appeared as shield-like plates with irregular margins, of a bluish-white color. Galindez [26] reports a case of bilateral cataract in a patient with scleroderma.

### Cataracts Produced by Toxins

*Galactose.*—Reiter and Lasky [27] present another case of the rare condition galactosemia and have made a general survey of the literature on this disease. Their patient, a 7-week-old white boy, had had a known abnormality of the liver since the age of 10 days and was admitted to the hospital because of failure to gain weight, irritability, abdominal swelling, edema, glycosuria, and bilateral lenticular opacities. When the infant was first seen, the cataracts appeared as sharp, lamellar opacities; 1½ weeks later they were more diffuse and spreading, although there was no involvement of the nucleus. At the age of 10 weeks, the cataracts were slightly less transparent, and small vacuoles appeared in the cortex near the equator. After the removal of galactose from the patient's diet, the cataracts began to regress, and eight weeks after the initial observation the lenses were normal. The author emphasizes the close parallelism between his case and the development of experimental galactose cataract in the rat.

*Toxins of Keratitis.*—Toxins in the anterior chamber due to keratitis with hypopyon may produce cataract. The nature of the lenticular changes observed in 10 such cases is discussed by Sbordone.[28]

### Injury to the Lens

*Contusion.*—In a discussion of ocular contusions, Hogan [29] mentions several types which may affect the lens. Spasm or paralysis of accommodation may occur as a result of irritation or severance of or damage to the ciliary nerves. Astigmatism may result from actual distortion, swelling, subluxation, or zonular tears. Luxation or subluxation is not uncommon, and in the author's opinion treatment is not indicated unless complications, such as cataract or glaucoma, intervene. Two types of lenticular opacities may follow contusion to the eye. These are the Vossius ring opacity, oftenest occurring after a blow to the cornea and usually due to blood pigment on the anterior capsule, and anterior and posterior subcapsular cataracts, due to capsular rupture or lens-fiber derangement.

*Foreign Body.*—François [30] describes his technique of removing foreign bodies from the lens without causing cataract formation. He removes the foreign body with an electromagnet through an incision at the limbus. A miotic is then used to contract the pupil, so that the iris will cover the capsular gap and dissolution of the lens fibers by the aqueous may be prevented.

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26. Galíndez Iglesias, F.: Catarata atópica, Arch. Soc. oftal. hispano-am. **11**:697-705, 1951; abstracted, Am. J. Ophth. **34**:1631, 1951.

27. Reiter, C., and Lasky, M. A.: Galactose Cataractogenesis: Review of Literature and Case Report, Am. J. Ophth. **35**:69-75, 1952.

28. Sbordone, G.: Rilievi clinici e considerazioni patogenetische sulle alterazioni del cristallino consecutive alle cheratiti suppurative con ipopion, Ann. ottal. e clin. ocul. **78**:17-24, 1952; abstracted, **35**:1234, 1952.

29. Hogan, M. J.: Ocular Contusions, Am. J. Ophth. **35**:1115-1124, 1952.

30. François, J.: Comment extraire les Corps étrangers du cristallin sans provoquer de cataracte? Ann. ocul. **185**:65-74, 1952.

### Radiation Cataract

*Human Radiation Cataract.*—Cogan, Donaldson, and Reese [31] have reviewed the clinical findings in 20 early cases of radiation cataract and have made histologic studies of 27 cases of radiation cataract in various stages of maturity. In the clinical group the cataracts were due to x- and gamma radiation, cyclotron radiation, and atomic-bomb radiation. The findings were remarkably similar in all cases, and the authors list the chief characteristic of the cataracts as "(1) the doughnut-shaped configuration, as seen with the ophthalmoscope, and (2) the sharply demarcated anterior boundary of the opacity and the bivalve configuration of the opacity, as seen with the slit-lamp biomicroscope." These characteristics are usually sufficient to distinguish radiation cataract from posterior polar cataract and cataracta complicata, with which it is most frequently confused. The histologic changes which the authors state to be less type-specific than the clinical signs are given as "(1) failure of the cells at the equator to differentiate into lens fibers, and (2) early migration of cells beneath the posterior capsule toward the posterior pole."

*Experimental X-Irradiation Cataract.*—Von Sallmann [32] has continued his studies on the role of cysteine in protecting against the damaging effects of x-radiation on the eye. He has now observed for an 18-month period a group of rabbits receiving 1,500 r of direct x-radiation to the right eye who were then treated with intravenous injection of cysteine and 30 minutes later received an equivalent amount of radiation to the left eye. Whereas advanced or total cataract was the invariable result in the control eyes, the lens changes in the left eyes were minimal and never sufficiently extensive to cause interference with observation of the fundus detail. They appeared as fine ring- or star-shaped opacities in the posterior cortex of an apparently stationary nature and were not unlike the opacities in the early stages of x-ray or radium cataract. Subconjunctival injections of cysteine over a period of three weeks did not influence the lens changes caused by irradiation after the intravenous use of cysteine. Subconjunctival administration of cysteine alone prior to irradiation exerted a moderate protective effect on the lens over an observation period of nine months.

Microscopic studies were performed on sections of lenses from both control and cysteine-pretreated rabbits who were killed two hours to three weeks after irradiation and before ophthalmoscopically visible cataracts had developed. A displacement of nuclei in the lens bow, cellular death, and nuclear fragmentation were seen more frequently and to a greater extent in the control eyes than in the eyes of the treated group. It appeared that cysteine therapy favorably influenced the recovery from inhibition of mitotic activity caused by the irradiation. The author emphasizes that since these early microscopic signs of lens damage were altered by the presence of a chemical substance, it is likely that indirect biochemical mechanisms of x-irradiation, and not direct hits, are at least in part responsible for these lesions.

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31. Cogan, D. G.; Donaldson, D. D., and Reese, A. B.: Clinical and Pathological Characteristics of Radiation Cataract, A. M. A. Arch. Ophth. **47**:55-70, 1952.

32. von Sallmann, L.: Abstract of Paper: Further Efforts to Influence X-Ray Cataract by Chemical Agents, A. M. A. Arch. Ophth. **47**:21-22, 1952; Experimental Studies on Early Lens Changes After Roentgen Irradiation: III. Effect of X-Radiation on Mitotic Activity and Nuclear Fragmentation of Lens Epithelium in Normal and Cysteine-Treated Rabbits, ibid. **47**:305-320, 1952; Further Efforts to Influence X-Ray Cataract by Chemical Agents, ibid. **48**:276-291, 1952.

Von Sallmann has also undertaken a study of cell division in the lens epithelium and the influence of irradiation on this function in rabbits some of which have been protected with cysteine. He found that the over-all mitotic index (ratio of the number of dividing cells to the number of resting cells) of the normal lens epithelium ranged from 18 : 100,000 to 27 : 100,000. There was great variation in the index, depending upon the zone. No mitosis was demonstrable in the nuclei of the lens bow, and mitosis was of low order in the meridional rows, in the zone between the rows and the germinative area, and in the central epithelium. The index was greatest in the germinative area and in the preequatorial zone. Older animals displayed indices below the young adult average, and very young animals, indices higher than the average.

The lens epithelium of eyes enucleated 30 minutes after direct irradiation with 1,500 r showed an almost complete inhibition of mitosis. Further experiments, in which the interval between irradiation and enucleation was prolonged, indicated that this suppression was of three to four days' duration and was followed by a recovery period, with normal mitotic activity attained on about the ninth day. There then followed a compensatory mitotic increase, lasting one or two weeks. During the phases of recovery and compensatory increase, structural alterations, more particularly nuclear fragmentation, were prominent, especially in the actively dividing cells of the germinative zone.

In the study of cysteine protection, the amino acid was injected in the same manner as in previous experiments, i. e., immediately after irradiation of the right eye and 30 minutes prior to irradiation of the left eye. Whereas previous studies had shown that pretreatment with cysteine favorably influenced all early microscopic visible signs of radiation damage to the lens, in the present experiment there was noted a complete suppression of mitosis in both eyes shortly after their exposure to 1,500 r, which lasted nine days. In general, the inhibition of cell division, recovery, and compensatory increase were little affected by cysteine pretreatment.

Glutathione and thiourea were found to be somewhat effective in protecting the lens against radiation damage, but to a less extent than was cysteine. Sodium thioglycollate and dimercaprol U. S. P. were ineffective. Pretreatment with dihydroxyacetone and *dl*-alpha-tocopherol, with citrovorum factor, and with cyanide did not reduce the damaging affects of 1,500 r to the eye.

Clark and Sykowski [33] have investigated the effects of high- and low-voltage x-irradiation on the incidence of lens opacities in mice. As a preface to their study, they summarize the physical differences between the two types as follows: 1. At voltages of less than 3,000,000 to 5,000,000 tissue ionization results from a disturbance of shell electrons, while at voltages higher than this, ionization results from changes within the atomic nuclei. 2. With low-voltage x-irradiation, ionization is maximal at the surface and decreases exponentially with increasing depth. With x-rays of approximately 5 mev or greater, ionization increases with increasing depth, reaches a maximum (the depth of which depends upon the voltage), and then decreases with increasing depth. 3. X-rays of 22 mev or greater induce radioactivity in tissues. In this study the effects of 124-kv. x-rays were compared with

33. Clark, L. B., and Sykowski, P.: Comparison of the Effect of Low (124 K. V.) and of High (50 MEV.) X Irradiation on the Incidence of Lens Opacities in Mice, Am. J. Ophth. **35**:848-850, 1952.

50-mev radiations (from the betatron), the distribution of ionization within the test organism being held as nearly the same as possible. The subjects were 5- to 6-week-old mice, and the whole body was exposed. Fifty weeks after exposure with a dose of 200 r, cataracts occurred in 80% with the 124-kv. machine and in 70% with the 50-mev machine. Cataract was produced in 95% with the 124-kv. machine and in 90% with the 50-mev machine. The authors believe that this slight difference is not statistically significant and that for similar doses the two methods produce similar effects. Thus, the different methods of ionization are not productive of different effects on the incidence of the lens opacities.

*Experimental Neutron Cataract.*—Cogan, Goff, and Graves [34] have investigated the production of cataracts by 14-mev neutrons from the Crockcroft-Walton Accelerator and by fission neutrons (polyenergetic, with a peak at 300 kev) from the Fast Reactor. In this study 10-week-old rabbits were subjected to a range of doses between $1 \times 10^{9}$ and $1 \times 10^{12}$ neutrons per square centimeter. The effects noted were essentially the same as in the radiation cataract produced by x-rays and consisted of epilation, keratoconjunctivitis, and cataract formation. The first two signs mentioned did not occur with doses lower than $1.5 \times 10^{11}$ neutrons per square centimeter and were of widely different intensities, depending on the dose. The early lens changes were of two varieties, described as vacuolar and granular. The former was a frequently transitory, and apparently reversible, change consisting of vacuoles in the region of the posterior horizontal suture just anterior to the posterior capsule. This change appeared prior to the granular change and was first noted at times from within several hours to two weeks after irradiation, depending upon the dose. The granular change consisted of small dots located along the posterior suture line and peripherally as a corona. The time of onset of this change varied from within a few days, with the higher doses, to several months, with the lower doses. Unlike the vacuolation, the granular change was apparently of a permanent nature. In general, the changes occurring in the lenses as a result of neutrons and x-rays displayed the same differences when high and when low doses were used, although it appeared that irradiation with 14-mev neutrons tended to produce more transient vacuolation than did the other types. The effectiveness of cataract production obtained with $8 \times 10^{9}$ neutrons per cubic centimeter (14 mev) or with $3 \times 10^{10}$ neutrons per cubic centimeter (fission energy) was approximately comparable to that obtainable with 500 r (1.2 mev).

*Experimental Ultrasonic Cataract.*—Lavine and co-workers [35] have undertaken a series of experiments in which the effects of ultrasonic radiation on excised calf eyes were observed. Ultrasonic waves are sound waves having a frequency beyond the audible range, i. e., above 30,000 cps. Earlier European reports indicated that ultrasonic radiation may be of possible benefit in the clearing of lenticular opacities, and it was with this hope that the investigations were initiated. Corneal opacities, an irreversible liquefaction of the vitreous and cataract were the chief effects pro-

34. Cogan, D. G.; Goff, J. L., and Graves, E.: Experimental Radiation Cataract: II. Cataract in the Rabbit Following Single Exposure to Fast Neutrons, A. M. A. Arch. Ophth. **47**:584-592, 1952.

35. Lavine, O.; Langenstrass, K. H.; Bowyer, C. M.; Fox, F. E.; Griffing, V., and Thaler, W.: Effects of Ultrasonic Waves on the Refractive Media of the Eye, A. M. A. Arch. Ophth. **47**:204-219, 1952.

duced. With low-frequency, high-intensity ultrasonic beams, the fine perinuclear lens opacities of Zeiss were reproduced. They are due to cavitation and are reversible. The authors believe that the mechanism involved in this type of opacity may offer a clue to the clearing of cataracts. In addition, a new type of cataract was produced by the use of high-frequency, high-intensity radiation. This type, which was an irreversible change, appeared to result from high local temperatures.

*Experimental Microwave Cataract.*—Richardson, Lomax, Nichols, and Green [36] have investigated the effects of 12.25-cm. microwaves of 100-watt output on rabbit lenses. Rabbits exposed at a distance of 6 in. (15 cm.) for 20 minutes did not have opacities within an eight-month period. When similar exposures were carried out at distances of 3.5, 3.75, and 5.0 cm., opacities developed within 2 to 14 days in 75, 50, and 25% of the animals respectively. Some lenses became cataractous rapidly and between daily inspections; other cataracts formed slowly over a period of several days. The latter first appeared as a translucent haze, which eventually took the form of scattered particles or threads of particles in a web-like structure between the posterior pole and the equator. Constriction or dilation of the pupil induced by the instillation of drugs did not appear to influence opacity formation. The authors also investigated the effects of subdamaging exposures to microwaves in the presence of alloxan diabetes. They hypothesized that if the two cataractogenic factors involved a disturbance of the same metabolic system, a summation effect might be expected. It is known that cataracts due to alloxan diabetes require 4 weeks or longer to make their appearance and that microwave cataracts appear within 15 days under the conditions imposed by the authors. A series of animals received 125 mg. of alloxan per kilograms of body weight and three to four days later one eye was irradiated with 12-cm. microwaves for 12 minutes at a distance of 5 cm. The dose of alloxan was considered low, but adequate for the production of cataract, while the microwave dose was definitely subdamaging. Of the 18 animals which survived this experiment, 6 exhibited cataract within 15 days, while their respective control eyes were normal. Ten animals failed to show cataract after three months. The authors are of the opinion that their findings indicate microwave cataract to be due to both increased ocular temperatures and a disturbance of the metabolic processes of the lens.

Daily and co-workers [37] have completed another study of the effects of microwaves on intact and enucleated rabbit eyes. Using thermistors inserted into the vitreous and into the orbit, they obtained the temperatures of the ocular tissues prior to and at intervals after exposure. Seventeen eyes of albino rabbits were exposed for durations of 10 to 30 minutes with a 94-watt output at a distance of 2 to 5 in. (5 to 12.5 cm.). Of these 17 eyes, cataract developed in 7. Of 17 eyes of pigmented rabbits exposed under the same conditions, cataract developed in only 3. The cataracts produced were of two types. One was a total cataract, present immediately after exposure and seen only with other grossly visible signs of ocular damage. The other appeared after an interval of several days to weeks and was limited to the posterior cortex.

36. Richardson, A. W.; Lomax, D. H.; Nichols, J., and Green, H. D.: Role of Energy, Pupillary Diameter, and Alloxan Diabetes in the Production of Ocular Damage by Microwave Irradiations, Am. J. Ophth. **35**:993-1000, 1952.

37. Daily, L.; Wakim, K. G.; Herrick, J. F.; Parkhill, E. M., and Benedict, W. L.: Effects of Microwave Diathermy on the Eye of the Rabbit, Am. J. Ophth. **35**:1001-1017, 1952.

CATARACT SURGERY

*Preparation of the Patient.*—Hyaluronidase; Curare: Tassman's [38] experience with hyaluronidase, which he used in association with procaine and epinephrine to improve akinesia, confirms the claims for its advantages in many previous reports. In cataract extraction, he recommends that a retrobulbar injection of hyaluronidase in 2% procaine solution be made not more than five minutes prior to corneal section. If the injection is done too early before the section, the degree of hypotony may be so great as to make the procedure somewhat more difficult. In cases of lens looping for dislocated lens and of cataract extractions in eyes with increased intraocular pressure, the addition of hyaluronidase to the procaine makes the procedure a less hazardous one. Hyaluronidase was also found to be of benefit in treating the postoperative edema and chemosis following cataract extraction.

Couadau and Campan [39] report on their use of curare in 100 cases of cataract surgery. They discuss in detail its beneficial effects on the orbicularis muscle, the extraocular muscles, the intraocular tension, and the vitreous. In all cases the eye was satisfactorily relaxed, and there were no instances of vitreous loss. In a report by Barraquer Moner,[40] a number of techniques of administration of curare are described, as well as the author's own, in which curare is the only anesthetic used. The author states that with its use the eye is relaxed, nystagmoid movements are absent, the vitreous recedes, and the pupil dilates after the section. He had no fatality among 1,000 cases.

*Operative Techniques.*—In an instructive article for the student, Atkinson [41] stresses the importance of daily practice in manual dexterity in the acquiring of a skilful surgical technique. He offers several novel suggestions as to how this may be accomplished in the absence of a cadaver or animal eyes and with the use of commonplace objects always readily available.

Katzin [42] has designed a new type of scissors for enlarging cataract sections which has the advantage that the handle may be held vertically and the slope of the usual type of incision avoided. Harrison [43] has devised a pair of scissors notched on its noncutting border for the removal of cataract sutures. After the suture is cut, the blade is rotated so that the knot is entangled in the serrations and the suture easily removed.

Roberts [44] describes a new technique for the burying of 6-0 mild chromic absorbable surgical (gut) corneoscleral sutures which he has used with complete satis-

38. Tassman, I. S.: Use of Hyaluronidase in Ophthalmology, Am. J. Ophth. **35**:683-686, 1952.

39. Couadau, A., and Campan: Introduction du curare en chirurgie oculaire: Considérations sur cent extractions de cataractes, Arch. ophth. **12**:48-57, 1952.

40. Barraquer Moner, J. I.: El uso del curare en cirugia ocular, Soc. oftal. hispano-am. **11**:683-696, 1951; abstracted, Am. J. Ophth. **34**:1778, 1951.

41. Atkinson, W. S.: Simple Practice Methods for Intracapsular Cataract Extraction, Am. J. Ophth. **35**:1167-1171, 1952.

42. Katzin, H. M.: A New Cataract Scissors, Am. J. Ophth. **35**:1353, 1952.

43. Harrison, W. J.: An Instrument for Removal of Eye Sutures, Am. J. Ophth. **35**:1207, 1952.

44. Roberts, W.: Buried Sutures for Closure of Cataract Incision, Am. J. Ophth. **35**:1459-1462, 1952.

faction in 62 consecutive extractions. Simonton [45] suggests a new type of combined bridle and conjunctival retraction suture for use in cataract surgery in which a sliding fornix-based flap is used. He states that one of its advantages is that the resultant effect of any pull on this suture is a tendency for the corneoscleral wound to close, rather than to gape. When sutures are used to expose the eye in cataract surgery, if the tarsal plate shows any tendency to eversion, Lytton [46] recommends that these sutures be placed perpendicularly to the lid margin. This gives a safe control of the lid and relieves the pressure of the outer canthus on the globe. Stallard [47] describes his modification of the McLean corneoscleral suture. He believes it valuable in the prevention of iris prolapse, separation of the wound edges, and hyphema.

Osmond [48] favors the keratome-and-scissors technique in cataract excisions over the Graefe-knife section. He states its only disadvantages are the introduction of two intruments into the eye, instead of one, and the slightly increased length of the procedure. Fine [49] has modified the simplified erysiphake, utilizing the suction principle of the fountain pen in order to give the instrument a higher degree of suction.

Kozlowski [50] recommends that for the extraction of an intumescent cataract the capsule be perforated at the superior pole, in order that a small amount of fluid may be released and the capsule grasped more easily.

Alvis and Alvis [51] describe the technique which they employed in 452 cataract extractions. The surgical routine in all cases included subconjunctival cocaine anesthesia (they regard retrobulbar injection as unnecessary and undesirable in most cases), Van Lint akinesia, lid retraction with the Guyton-Pars speculum, and fixation with a modified Falcão scleral forceps. In all cases, prior to opening of the chamber, a modified corneoscleral mattress suture was placed through the edges of a preformed groove. In 237 cases a fornix-based flap was prepared; in 215 cases no flap was used. Three corneoscleral sutures were used in 301 cases, and only one suture was used in 151 cases. The incision was made with a Graefe knife and the lens intracapsularly extracted through a round pupil, when possible, with either the Arruga forceps or the Bell erisiphake. According to the authors, the results of the study demonstrated the great effectiveness of corneoscleral sutures in wound closure. The incidence of wound opening and iris prolapse was found to be less if three corneoscleral sutures were used than if only one was used. The authors believe in the efficacy of the preplaced mattress suture they described as a guard against loss of vitreous. They express the opinion that a fornix-based conjunctival flap is of little value in wound closure.

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45. Simonton, J. T.: A Combined Bridle and Conjunctival Retraction Suture, Am. J. Ophth. **35**:707-708, 1952.

46. Lytton, H.: Lid Sutures in Cataract Surgery, Am. J. Ophth. **35**:105-106, 1952.

47. Stallard, H. B.: A Corneoscleral Suture in Cataract Extraction, Brit. M. J. **2**:88-90, 1951.

48. Osmond, A. H.: Keratome and Scissors, Brit. J. Ophth. **35**:406-408, 1951.

49. Fine, M.: An Improved Manually Operated Erysiphake, A. M. A. Arch. Ophth. **47**: 513-514, 1952.

50. Kozlowski, B.: A Method of Extracting an Intumescent Cataract, Klin. oczna **21**:215-216, 1951; abstracted, Am. J. Ophth. **35**:1066, 1952.

51. Alvis, B. Y., and Alvis, E. B.: Wound Closure in Cataract Surgery: A Modified Corneoscleral Suture, Am. J. Ophth. **35**:967-976, 1952.

Ridley [52] describes a new operation in which an artificial acrylic lens is inserted into the eye after cataract extraction. Of 27 patients, the majority of whom had monocular cataract, 24 were considered to have a satisfactory surgical result, with the lens in good position, normal tension, and no evidence of inflammation. A number of eyes showed some exudate and iris pigment on the lens surface, which partially obstructed vision, but there appeared to be gradual improvement in this type of complication. In the eyes tested for visual acuity thus far, the following results were obtained: 6/36, in 2 eyes; 6/24 in 1 eye; 6/18 in 3 eyes; 6/12, in 2 eyes; 6/9, in 5 eyes, and 6/5, in 2 eyes. With the artificial lens, the difference in refraction in the two eyes is usually within 2 D., a value which is quite compatible with binocular vision. Arruga [53] reports nine cases in which he employed Ridley's operation. He warns that the iris must not be atrophic or rigid, or the lens may dislocate posteriorly in the vitreous. He noted pigmentation on the anterior surface of the lens and some synechia formation. He, too, found that the former complication usually improved after a few months.

Vail,[54] in a recent publication, discusses the proper technique of lens removal in the light of modern knowledge of the structure of the zonular attachments. This paper contains much valuable practical information regarding the development, anatomy, and biomicroscopy of the zonules. The author states that excessive pull on the lens capsule during intracapsular extraction may produce one or all of three complicating effects. 1. Because of the strong capillary attraction between the anterior hyaloid membrane and the lens in Berger's retrolental space (hyaloid fossa), the probability that the ligamentum hyaloideocapsulare of Wieger is an actual structure, and the possibility of the existence of embryonic adhesions, holes in the anterior vitreous may be produced which can lead to vitreous herniation. 2. Retinal tears in the region of the fragile ora serrata of the aged may result, since the pull is transmitted through the lens to the zonules attached at that site. 3. The probable intimate connection of the zonules and the vitreous makes possible a vitreous detachment at the ora, which may predispose to later retinal detachment. Expression, rather than traction, therefore, is the most desirable procedure, although pure expression is hazardous. The author states that if the lower edge of the lens is tilted forward and the lens then rotated gently from side to side, the following desired effects are accomplished: The capillary attraction in Berger's space is abolished; adhesions between the hyaloid membrane and the posterior capsule are gently ruptured, and the zonular membrane is drawn taut. At this point, limbal pressure directed backward and down in a milking fashion will cause a separation of the zonules from the lens.

Technique in the One-Eyed Patient: Callahan [55] has presented a study of 103 cases of cataract extraction in the one-eyed patients. He recommends that when extraction is contemplated on the remaining eye of such a patient, a careful investi-

52. Ridley, H.: Intra-Ocular Acrylic Lenses, Brit. J. Ophth. **36**:113-122, 1952; Intra-Ocular Acrylic Lenses after Cataract Extraction, Lancet **1**:118-121, 1952.

53. Arruga, A.: Problems inmediatos de la inclusión de la lente de Ridley, Arch. Soc. oftal. hispano-am. **11**:1490-1507, 1951; abstracted, Am. J. Ophth. **35**:1232, 1952.

54. Vail, D.: Zonule Membrane and Cataract Expression, A. M. A. Arch. Ophth. **48**:405-413, 1952.

55. Callahan, A.: Cataract Extraction in the One-Eyed Patient: A Study of 103 Consecutive Cases, Am. J. Ophth. **35**:1285-1290, 1952.

gation be undertaken to determine the causes of loss of the first eye. In his series, 36 first eyes were lost because of complications following cataract extraction; 26, as a result of primary glaucoma; 23, as a result of physical trauma, and the remainder, for a variety of causes, notably corneal degeneration. Using the round-pupil intracapsular extraction, with peripheral iridotomy, and two preplaced corneoscleral sutures, the author was able to avoid in the second eye the complication that destroyed the first eye in all but one case of retinal detachment and in four cases of corneal dystrophy. In 75% of the cases there was a final visual acuity of 20/40 or better. He suggests that in cases in which retinal detachment developed after cataract extraction in the first eye and in which peripheral cystic degeneration is observed in the second eye, a circle of surface diathermy applications be made to the sclera over the ora serrata approximately two months before operation is planned.

*Technique in Cataract Extraction After Glaucoma Surgery.*—Callahan [56] also presents the results of his method of dealing with cataract extraction after glaucoma surgery. He used the lateroinferior approach in 15 cases in which trephination had been performed for glaucoma from four months to 11 years previously. He avoided sectioning through the bleb because of the possibility of interference with its filtration. Section was likewise not made through the clear cornea anterior to the bleb because of the technical difficulties in removing the intact lens from such an overhanging shelf and because of the dangers of pupillary cornea scarring. In an analysis of his results, vision was limited to perception of hand movements or less in four cases, was 20/60 to 20/100 in five cases, and was 20/40 or better in six cases. He expresses the opinion that the chief factor in the final visual result is the previous damage done to the eye by the glaucoma.

*Wound Healing.*—Dunnington and Regan [57] have extended their study of ocular wound closure with an analysis of the effect of sutures and fibrin on healing. Using rhesus monkeys, they employed nonabsorbable (silk) and absorbable (gut) surgical sutures for cataract incisions, both with and without conjunctival flaps. The following histologic effects were noted: (1) a proliferation of conjunctival or corneal epithelium along the tract of the suture; (2) slight round-cell infiltration in the vicinity of the suture, and (3) stromal necrosis and decreased fibroblastic proliferation around the suture. They state that deeply placed sutures, especially if not removed early enough, could result in such abnormalities in healing as epithelization of the anterior chamber, fistulization, incarceration or prolapse of the iris, and hemorrhage into the anterior chamber. The authors advise, therefore, that corneoscleral sutures not be inserted to a depth greater than one-half the depth of the incision and that they be removed within 12 days. When fibrin was used to seal the cataract incisions (in the absence of any sutures), histologic examination two days later showed the presence of fibrin plug, preventing good approximation of the wound edges, absence of fibroblastic proliferation, and in an occasional instance, epithelization between the lips of the wound. Two days later some fibroblasts had made their appearance, but the epithelial proliferation had advanced. At the end

56. Callahan, A.: Cataract Extraction After Glaucoma Surgery: Lateroinferior Approach Following Filtering Glaucoma Operation, A. M. A. Arch. Ophth. **47**:132-140, 1952.

57. Dunnington, J. H., and Regan, E. F.: Effect of Sutures and of Thrombin upon Ocular Wound Healing, Am. J. Ophth. **35**:167-177, 1952.

of one week fibroblastic proliferation was sufficiently extensive to form a broad scar, which extended throughout the wound. Although the use of fibrin appeared to prevent the round-cell infiltration and necrosis associated with sutures, the authors do not think that fibrin is an entirely satisfactory agent for closure, as it causes separation of the wound edges, creates a broad scar, which lacks the tensile strength of normal tissue, and may result in epithelization of the wound edges in cases in which a corneal incision is performed.

### Complications of Cataract Surgery

*Statistics from a Large Series.*—Townes, Moran, and Pfingst [58] report on the results of 565 cataract extractions. All types of cataract are included except congenital and traumatic. The general procedure consisted in the use of preplaced nonabsorbable (silk) or absorbable (gut) surgical sutures and phacoerysis, after the manner of Castroviejo. In this series of 565 eyes, 127 were involved in 220 operative or postoperative complications. The most frequent of these were vitreous loss (37 cases), uveitis (33 cases), glaucoma (33 cases), capsular rupture (21 cases), secondary membrane (16 cases), delayed re-formation of the anterior chamber (15 cases), hemorrhage (14 cases), detachment of the retina (12 cases), and keratitis (11 cases). Sixty-eight of the 127 eyes with complications have recovered sufficient vision to enable the patient to read.

*Bullous Keratopathy.*—Sternberg and Meyer [59] reported four cases in which previous operation for acute glaucoma had been performed and in which bullous keratopathy resulted when intracapsular cataract extraction was later performed in a different quadrant. They suggest that the keratopathy results when the corneal endothelium, already somewhat impaired from the acute glaucoma and its necessary surgical treatment, undergoes further damage through interference with its blood supply in a new limbal area during cataract surgery. They recommend that when cataract surgery becomes necessary after a filtering operation for glaucoma, a limbus-based conjunctival flap be made to either side of the bleb area and that two McLean corneoscleral sutures be inserted to each side several millimeters from the bleb. The incision in the region of the previous glaucoma surgery is in the cornea and anterior to the bleb.

*Lint in the Chamber.*—Vail [60] describes three cases in which lint was accidentally introduced into the anterior chamber during cataract extraction. In each case iritis ensued, leading to the formation of posterior synechia. The author discusses the precautions which must be observed to minimize the chances of such foreign material as lint, cilia, talc, oil droplets, and pieces of rubber finding its way into the eye.

*Lens-Cortex Retention.*—Much [61] recommends that in cases in which large masses of lens material remain after extracapsular extraction ultrashort wave therapy be administered to the eye to hasten the absorption.

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58. Townes, O. D.; Moran, C. T., and Pfingst, H. A.: Complications of Cataract Surgery, Am. J. Ophth. **35**:1311-1319, 1952.

59. Sternberg, P., and Meyer, S. J.: Corneal Dystrophy Following Secondary Intraocular Operations, A. M. A. Arch. Ophth. **46**:527-530, 1951.

60. Vail, D.: Lint in the Anterior Chamber Following Intraocular Surgery, Am. J. Ophth. **34**:1533-1538, 1951.

61. Much, V.: Ultro-Kurzwellen-Therapie in der postoperativen (extrakapsulären) Cataract-Behandlung, Ophthalmologica **121**:41-43, 1951.

*Iris Prolapse.*—Potter [62] used cortisone therapy locally in a case in which it was necessary to postpone treatment of iris prolapse complicating cataract extraction. At no time was there any irritation of the iris.

*Inflammation.*—Iridocyclitis and endophthalmitis following cataract extraction were successfully treated, by Agatston [63] with a combination of locally and systemically administered cortisone.

*Corneal Curvature.*—Floyd [64] studied the changes in corneal curvature as measured by the keratometer at intervals following cataract extraction in 47 cases in which corneoscleral sutures were employed. After one month, in approximately 60% of his cases, there were an increase in the radius of curvature of the more nearly vertical meridian and a decrease in the radius of curvature of the more nearly horizontal meridian, a change which has long been recognized. What is new and of interest in his observations, however, is that in these same cases a marked astigmatism was present 10 days after operation with the axis of increased radius of curvature in the more nearly horizontal meridian and a decreased radius of curvature in the more nearly vertical meridian. This phenomenon disappeared with the removal of the sutures, and the author concludes, therefore, that it was primarily due to the sutures. The average amount of change in the astigmatism was greatest during the first month after operation, but some change was still noted at the end of six months. Because of this, he suggests that it is inadvisable to prescribe permanent glasses at the end of two months. In general, the corneal curvature is of the same type as was present after operation, with a tendency to a relative increase in the vertical radius of curvature, possibly due to an incomplete reapposition of the corneal flap. There was demonstrated a slight tendency to increased flattening of the cornea in its spherical equivalent, especially in cases in which there was loss of vitreous during operation.

*Carcinoma.*—Oliver and Roberts [65] report the rather unusual occurrence of an epidermoid carcinoma of the bulbar conjunctiva, which developed at the inferior extremity of the arched conjunctival incision made for cataract extraction. The tumor was first noticed approximately six weeks after uneventful extraction and appeared as a small, whitish-yellow, warty mass, which was readily excised. There was no evidence of recurrence 10 months later.

*Vitreous Changes.*—Briggs [66] reports an adhesion of the vitreous to the posterior surface of the cornea which followed cataract extraction and which he successfully freed by the injection of air into the anterior chamber.

Harrington [67] has made a study of the late changes in the vitreous which occurred in 66 selected cases of intracapsular extraction. The interval following extraction

62. Potter, W. B.: Cortisone Therapy in Anterior-Segment Inflammation, Am. J. Ophth. **34**:1650-1654, 1951.

63. Agatston, H.: Use of Cortisone in Ocular Conditions, Am. J. Ophth. **34**:1655-1664, 1951.

64. Floyd, G.: Changes in the Corneal Curvature Following Cataract Extraction, Am. J. Ophth. **34**:1525-1533, 1951.

65. Oliver, D., and Roberts, W.: Carcinoma of the Bulbar Conjunctiva Following Cataract Extraction: Report of a Case, A. M. A. Arch. Ophth. **47**:78-80, 1952.

66. Briggs, H. H.: Method of Treating Vitreous Adhesion to Cornea, Am. J. Ophth. **35**: 411-412, 1952.

67. Harrington, D. O.: Late Changes in the Vitreous Following Uncomplicated Intracapsular Cataract Extraction, Am. J. Ophth. **35**:1177-1184, 1952.

varied from 9 days to 11 years, with an average of 2 years 3 months, and in all cases there were an absence of complications of any sort and a postoperative visual acuity of 20/20 or better. There was no uniform operative procedure. The author lists the changes in the vitreous as follows: simple herniation through the pupil; herniation with potential glaucoma due to pupillary block from iris-hyaloid membrane adhesions; herniation with persistent contact of the vitreous-cornea, leading to bullous keratitis; absence of the vitreous face; holes in the anterior hyaloid membrane, thickening and opacification of the anterior face of the vitreous, and posterior vitreous detachment. Harrington concludes that the aforementioned changes have no deleterious effect on the functioning of the eye, with three possible, but apparently uncommonly occurring, exceptions: 1. Persistent contact of the vitreous with the cornea may give rise to bullous keratitis. 2. Opacification and thickening of the anterior face of the vitreous may cause some degree of visual loss. 3. Glaucoma due to pupillary block may occur when herniation of the vitreous is accompanied by an annular posterior synechia between the iris and the hyaloid membrane. The method of lens extraction does not appear to affect the late changes in the vitreous. Vitreous-cornea contact, however, appears to be less common in round-pupil operations; the injection of air into the anterior chamber is a further aid in prophylaxis.

*Retinal Detachment.*—Coles and Laval[68] present an instructive case of retinal detachment which followed operation for cataract associated with neurodermatitis. A white woman aged 34 had a history of bouts of neurodermatitis, frequently related to emotional stress, since childhood. At the time of her first examination, she had a ripe anterior subcapsular cataract with pronounced cortical opacification in the left eye and incipient anterior and posterior subcapsular changes in the right eye, although vision in the latter was 20/20. In a period of but a few months vision in the right eye diminished from 20/20 to 20/100. (There were indications that the cataractous changes in the left eye had undergone a similarly rapid course.) An extracapsular cataract extraction in the left eye was followed by intractable iridocyclitis, and within one month by retinal detachment, which did not respond to surgical treatment. Approximately six months later, vision in the right eye was reduced to 10/200, and extracapsular extraction was performed on this eye, with the same results of iridocyclitis and retinal detachment. In surveying the literature, the authors found 63 cases of cataract associated with neurodermatitis. Of these, the results following cataract extraction were unfavorable in 36%, and in 22% the poor outcome was due to detachment. The authors express the opinion that detachment results from "an unhealthy vitreous which does not hold the retina in place." They urge that in this type of cataract periodic examination be made of the vitreous, of the retina for subclinical tears, and of the visual fields. Surgical intervention should be of the most conservative type, so as to cause as little disturbance to the vitreous as possible; in persons below the age of 30, needling and linear extraction should be considered.

Zanek[69] has recently reported a case of successful cataract extraction in a man aged 25 who had the typical cataract of neurodermatitis.

68. Coles, R. S., and Laval, J.: Retinal Detachments Occurring in Cataract Associated with Neurodermatitis, A. M. A. Arch. Ophth. **48**:30-39, 1952.

69. Zanek, O. L.: Atopic Cataract: A Case Report, Texas J. Med. **47**:294-297, 1951.

### Reactions of the Eye to Lens Substance and Cataract

*Animal Experimentation.*—Using albino rabbits as subjects, Müller[70] has recently investigated the nature of phacogenetic ophthalmia. He states that it is an inflammation caused by lens material that has been freed from the capsule and that it is characterized by an intensified, hyperergic reaction of the entire anterior portion of the eye. The reaction in the posterior section of the eye completely recedes, even in the most serious cases. He states that panophthalmitis never occurs, as it does after bacterial infection. The histiocytic reaction was particularly pronounced; leucocytes were predominant only at the inception of the inflammation or in special circumstances. He found that the intensified reaction of phacogenetic ophthalmia can be produced in animals by sensitization against heterologous, homologous, and autologous lens material. Since he also injected, as an adjuvant, attenuated tubercle bacilli, it is probable that in these instances a combination allergy was produced. There are not sufficient reasons for interpreting the reaction as a simple albumin anaphylaxis. Such a reaction may, of course, be produced and its nature may be ascertained by precipitation of the circulating antibodies, but it is apparently only occasionally the exclusive cause of ophthalmia phacogenetica. The extent to which the reaction involved infection allergy or the Shwartzman phenomenon was undecided.

*Clinical Cases.*—Irvine and Irvine[71] present 20 cases of ocular disease resulting from the presence of disorganized lens tissue within the eye. They classify their cases under the following heads: endophthalmitis phacoanaphylactica, phacotoxic inflammation, and "phacogenetic" glaucoma (open iridocorneal angle). The pathognomonic finding in the first category is the combination of polymorphonuclear leucocytes, macrophages, and giant cells phagocytosing lens material. Additionally, there may be precipitates on Descemet's membrane and a cyclitic membrane. The posterior segment is relatively unaffected. In all the authors' cases, the disease was associated with immature cataractous lens material dispersed in the eye after operation for senile cataract or as a result of injury to the eye (traumatic cataract). In the second category the pathologic process consists in a pronounced plasma-cell and macrophage response in the iris and the ciliary body, accompanied by lardaceous deposits on the retina and on Descemet's membrane. Clinically, a hypermature cataract is present, the degenerated liquid products of which account for the high protein content of the aqueous. In the third classification the cataractous lens is likewise hypermature. A seepage of lens material through the capsule, although resulting in little inflammatory response, stimulates the production of large monocytic macrophages, which obstruct the drainage channels of the eye.

The authors call attention to the following pertinent points: 1. In all the above-mentioned conditions, since the posterior segment is relatively uninvolved, the eye may be saved by removal of the lens or the lens remnants. Faulty light projection does not contraindicate this treatment or preclude the chances of a good result.

70. Müller, H.: Tierexperimentelle Untersuchungen zur Ophthalmia phakogenetica, von Graefes Arch. Ophth. **153**:1-35, 1952.

71. Irvine, S. R., and Irvine, A. R., Jr.: Lens-Induced Uveitis and Glaucoma: I. Endophthalmitis Phaco-Anaphylactica; II. The "Phacotoxic" Reaction; III. "Phacogenetic Glaucoma"; Lens-Induced Glaucoma; Mature or Hypermature Cataract; Open Iridocorneal Angle, Am. J. Ophth. **35**:177-186, 370-375, 489-499, 1952.

2. Uveitis or glaucoma occurring in patients with mature or hypermature cataract should lead one to consider the lens as the etiologic agent. The presence of large keratic precipitates and the finding upon paracentesis of a high protein content of the aqueous, with cells and particulate matter, are substantiating factors in the diagnosis. 3. In persistent uveitis following extracapsular cataract extraction or injury to the eye, especially when there has been a sudden increase in large keratic precipitates, paracentesis and irrigation of the anterior chamber are indicated. 4. It may be necessary to differentiate a reaction to lens materials and sympathetic ophthalmia. This occurs when after surgery or injury in one eye a cataract in the other eye causes coincidental reaction to lens substance. A tentative diagnosis of lens-induced uveitis is justified only in cases in which the lens is mature or hypermature, since only in these cases is leakage through the capsule likely. Irrigation of the anterior chamber to remove lens remnants will aid in the diagnosis.

## THE VITREOUS

*Structure.*—Bembridge, Crawford, and Pirie [72] have used the phase microscope to study the vitreous of the ox, pigeon, and monkey. In the ox vitreous they observed the following three structures: (1) coarse branching fibers attaching the vitreous body at its base, (2) fine parallel fibers coursing through the main body of the vitreous, and (3) a hyaline membrane enclosing the vitreous. In the pigeon vitreous, no coarse branching fibers could be seen, and the vitreous appeared so granular that it was difficult to tell whether fibers were present. The monkey vitreous showed the same two types of fibers seen in the ox, but a hyaline membrane could not be demonstrated. Experiments with enzymes indicated that the coarse branching fibers of the ciliary region are digested by trypsin and unaffected by collagenase. The fine parallel fibers in the main vitreous mass were liquefied by collagenase but unaffected by trypsin.

Grignolo [73] has studied the microscopic and submicroscopic structure of the fresh vitreous body in human and cattle eyes. Using the phase microscope, he demonstrated in the posterior vitreous branching fibers of considerable length running in a meridional direction and approximately parallel to the surface of the vitreous. The branches, which tapered into fibers of smaller width, ramified in every direction and anastomosed with each other to form a network, through the interstices of which a second network, of still thinner fibers, could be seen. Anteriorly in the vitreous, fibrous bundles were detected, formed of closely interlaced fibers which originated from the vitreous base and eventually separated from each other. These bundles attached to another system of fibers, which ran parallel with and anterior to the ora serrata and vitreous base. The vitreous body was observed to be surrounded by a homogeneous, transparent surface layer. Investigations of the submicroscopic vitreous structures, as carried out with the electron microscope, were summarized in last year's survey. The three types of fibrils identified with this instrument in fragmented vitreous sediment are (1) a type which appears to be collagen, (2) a type which is apparently a collagen-like material, and (3) a type, the most abundant, the nature of which is unknown.

72. Bembridge, B. A.; Crawford, G. N. C., and Pirie, A.: Phase-Contrast Microscopy of the Animal Vitreous Body, Brit. J. Ophth. **36**:131-142, 1952.

73. Grignolo, A.: Fibrous Components of the Vitreous Body, A. M. A. Arch. Ophth. **47**: 760-774, 1952.

*Chemistry.*—In mammals, de Vincentiis [74] founds a marked difference in the concentration of lactic and pyruvic acids between the vitreous and the plasma (150 to 250%), whereas in amphibia and fishes the difference was only about 15%. Both acids were far higher in concentration in the vitreous than in the plasma.

*Contusion.*—Hogan,[29] in a discussion of ocular contusions, mentions the damage that may occur in the vitreous as a result of a blow, or as a result of the outpouring of edema fluid, cellular exudate, and hemorrhage. The hemorrhage usually becomes organized by connective tissue from the ciliary body and retina, with resulting visual loss, and there are frequently shrinkage and detachment of the vitreous. The author states that in the case of a slowly absorbing large hemorrhage, in the absence of other contraindications, a vitreous replacement should merit consideration.

*Detachment.*—De Vries [75] describes five cases of spontaneous and sudden posterior detachment of the vitreous associated with multiple minute retinal hemorrhages near the optic disk. These are apparently due to the microtrauma of the retina at this point. Adamantiadis [76] reports 26 cases of posterior annular detachments of the vitreous. In these cases the typical picture was that of a circular membrane, about the size of the papilla, which folded and unfolded with the movements of the eye. Over an observation period of four years, retinal detachment developed in only one case in the 26. The author believes the condition to be a degenerative change associated with myopia or aging. Costi [77] reports five cases of diminished vision due to detachment. There were liquefaction, white spots, and a band of increased density in the posterior vitreous in all cases. It is the author's belief that the condition is due to posterior uveitis and that the prognosis is good if therapy is directed toward its eradication. Schepens [78] mentions the alterations in the vitreous occurring in subclinical retinal detachment. The most conspicuous of these was a small or moderate amount of hemorrhage, observed in 12% of his series.

*Clearing of Vitreous Opacities.*—Gordon and co-workers [79] state that the vitreous exudation associated with uveitis is frequently cleared with either local or systemic cortisone therapy. Agatston [63] successfully treated an eye with vitreous exudation by means of subconjunctival injection of cortisone, with clearing of the vitreous in 10 days. Eggers [80] recommends the ingestion of lipotropic substances for the benign vitreous opacities unassociated with ocular inflammation or other foci of infection.

30 N. Michigan Ave. (2).

74. de Vincentiis, M.: Ulteriori osservazioni sul contenuto di acido piruvico e acido lattico nel vitreo, Boll. Soc. ital. biol. sper. **27**:309-312, 1951; abstracted, Excerpta Med. XII **6**:173, 1952.

75. de Vries, S.: Retinal Haemorrhages in Posterior Vitreous Detachment, Ophthalmologica **122**:245-248, 1951.

76. Adamantiadis, B.: Décollement annulaire postérieur du vitré et sa relation avec le décollement de la rétine, Arch. opht. **11**:457-461, 1951.

77. Costi, C.: Errores diagnósticos por deficiente exploracion del vitreo posterior, Arch. Soc. oftal. hispano-am. **11**:142-147, 1951; abstracted, Am. J. Ophth. **34**:1634, 1951.

78. Schepens, C. L.: Subclinical Retinal Detachments, A. M. A. Arch. Ophth. **47**:593-606, 1952.

79. Gordon, D. M.; McLean, J. M.; Koteen, H.; Bousquet, F. P.; McCusker, W. D.; Baras, J.; Wetzig, P., and Norton, E. W. D.: Use of ACTH and Cortisone in Ophthalmology, Am. J. Ophth. **34**:1675-1686, 1951.

80. Eggers, H.: Lipotropic Substances for the Absorption of Vitreous Opacities, New York J. Med. **51**:2255-2256, 1951.

# Society Transactions

## COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

George F. J. Kelly, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

*Oct. 23, 1952*

**Orbital Implant with Additional Material at the Upper Pole.** Dr. Wilfred E. Fry.

This is not an implant to end all implants. It is a method of implantation to be added to the long list of others. The extent of its usefulness is yet to be determined.

It has one feature of interest. A small amount of material has been added to the upper pole of an implant that I have used at various times, beginning about six or eight years ago. The purpose is to make easier the fitting of a prosthesis so that the appearance of the upper lid may be more acceptable.

The implant is fully covered by Tenon's capsule and by conjunctiva. The amount of rotation is not noteworthy. This amount will vary with the skill of the fitting of the prosthesis and with the surgical care.

The implant is based on a 16-mm. plastic sphere. The anterior face has been cut off to give a flat anterior surface. At the superior pole a 2-mm. addition has been made. This is blended with the curve of the sphere. Four oblique tunnels, 3mm. in diameter, are drilled through the sphere, to meet on the anterior surface. All edges are rounded slightly and rendered smooth. The size of the implant may be varied by using an 18-mm. or a 14-mm. sphere. The 16-mm. sphere is the most useful; the 18-mm. sphere is the largest that has been found useful.

In the surgical procedure, care should be used in overlapping the muscles, silk sutures being used on one and surgical gut sutures on the other of the two opposing muscles. A deep anchor suture should be placed at the inner and outer ends of the conjunctiva. This helps to deepen the sac at these points. Tenon's capsule and the conjunctiva should be sutured horizontally, but at slightly different levels.

The first prosthesis can be fitted in two weeks.

I have not searched the literature to determine how many similar implants have been devised. I may merely be describing again something used 50 years ago.

**Use of the Newer Anesthetic Drugs in Ophthalmology.** Dr. Hrant H. Stone.

The use of morphine in ophthalmic surgery was considered. Morphine is a valuable drug. The nausea and vomiting associated with its use do not represent sensitivity to the drug. Nausea and vomiting are more frequent in the ambulatory patient, and more frequent when large and multiple doses are employed and when food is present in the stomach. These observations apply also to the morphine substitutes, such as methadon, dihydromorphine (dilaudid®), and meperidine (demerol®). These observations were applied to the use of morphine in ophthalmic surgery.

The currently used local anesthetic agents for topical infiltration and regional anesthesia were evaluated. Various adjuncts to local anesthesia, such as the use of vasopressor drugs, hyaluronidase, and curare, were discussed and evaluated. The disadvantages and limitations of local anesthesia for ophthalmic surgery were noted.

The use of general anesthesia for ophthalmic surgery was next considered. Among the factors stressed were the importance of preoperative medication, the advantages and disadvantages of the various anesthetic agents employed, and the adjuncts of advantage when general anesthesia is used. General anesthesia is only as safe as the skill of the administrator. The selection of the agent, whether it be a drug administered by inhalation or given intravenously or rectally, is not of primary importance if the anesthetist is competent. General anesthesia can be used for ophthalmic surgery far more extensively with the advent of the professional anesthetist and the newer

improvements in technique. General anesthesia should not be refused the ophthalmic patient if an indication exists for its use. Such an indication usually depends upon two factors: the choice of the surgeon and the cooperativeness of the patient. Unless specifically contraindicated, the drug for general anesthesia in ophthalmic surgery should always be administered through an endotracheal catheter. Only in this manner can the two primary dangers of general anesthesia, i. e., respiratory obstruction and respiratory depression, be effectively combated.

The use of thiopental sodium was discussed in detail. It was concluded that this drug is an excellent agent when used with care. The complications associated with its use, namely, laryngospasm and respiratory depression, can be overcome by using an endotracheal tube.

The complications of general anesthesia were listed, and their significance was discussed.

DISCUSSION

Dr. Edmund B. Spaeth: Several points were stressed. 1. Absolute dependence upon the anesthetist is most important. 2. Preoperative preparation is very important. Most mistakes and accidents in ophthalmic surgery connected with anesthesia are the result of poor preoperative preparation—too much routine and not sufficient consideration of the individual patient. 3. The choice of general or local anesthesia should be made carefully. A long and extensive procedure, such as retinal-separation surgery, plastic surgery, and lacrimal-sac surgery, takes time for proper performance, and the surgeon should not be hurried. The anesthetist should be asked to check the patient and utilize his expert knowledge. 4. Hyaluronidase is without doubt most important in proper local anesthesia. 5. So many factors of importance arise in connection with muscle surgery at the time of the operation that general anesthesia is necessary in all but the occasional case.

Dr. George F. J. Kelly: What are the danger signs in the intravenous use of thiopental sodium? The texts on pharmacology are not very clear on this; they state that one must depend on the experience of the anesthetist. Dr. Stone, what would be your choice of anesthesia if you had to have ophthalmic surgery yourself?

Dr. Hrant H. Stone: Respiratory depression and apnea are the primary dangers in the use of thiopental sodium. Respiratory depression is not of serious consequence to the experienced anesthetist. It is possible to oxygenate a patient perfectly and remove carbon dioxide by artificial respiration during apnea while still maintaining a stable blood pressure. This can be done, however, only if the anesthetist has complete control of the patient's airway by the use of an endotracheal tube and if the apparatus is available by which manual inflation of the lungs with oxygen can be achieved. It is believed that the use of thiopental sodium for ophthalmic surgery, especially cataract surgery, is safe if these requirements are met. During cataract surgery it is vital to have a quiet patient. Straining, coughing, or sneezing must not occur. The use of thiopental sodium, which depresses respiration and prevents such complications, is justified in the hands of the qualified anesthetist.

Laryngospasm is the other real danger when one is using thiopental sodium. Its development can be fatal. Laryngospasm usually occurs when the patient is under light thiopental narcosis and can be prevented or minimized if larger doses of the drug are employed prior to the initiation of stimuli which can evoke such a reflex. Laryngospasm can be prevented by the use of an endotracheal tube. It is believed that the use of an endotracheal tube is vital to the safe conduct of any ophthalmic procedure, especially an intraocular one, when one is using general anesthesia with thiopental sodium.

If I had to have a cataract extraction, I perhaps should prefer local anesthesia; however, I should not hesitate to have general anesthesia with thiopental sodium if I knew the qualifications of the anesthetist and felt that an indication existed for its choice.

**Monocular Aphakia.** Dr. Alfred Cowan.

On removal of the crystalline lens an entirely new kind of vision is provided—probably as acute as before or more so, but with magnified images, no accommoda-

tion, greater aberration, lessened focal depth, and a changed pupil, which allows a different quantity and quality of light to enter the eye. The aphakic eye is so different that it cannot possibly be paired with a normal, dynamic eye to make a workable team, whether it is corrected with a spectacle lens, a contact lens, or a minifying lens. Many claims have been made that good single binocular vision, from infinity in to 10 in. (30 cm.) for aphakic patients of all ages, even very young persons with good accommodation in the phakic eye, has been obtained by the use of a contact lens, and that the retinal image is then of the same size, or nearly the same size, as that in the other, the normal, eye.

Mere absence of diplopia does not indicate single binocular vision. Careful examination in such cases of monocular aphakia will show that there is at best a spurious kind of binocular vision—nothing more than that the patient has learned to disregard entirely the image of one or the other eye. A one-eyed person is not necessarily unhappy, and not seriously handicapped. He may do well in most occupations and in many sports. A one-eyed person can have a considerable sense of depth and solidity and can judge distance. For direct vision one eye is just as good as two.

Of course, two eyes with good, comfortable single binocular vision are better than one. Stereopsis is an advantage, and to acquire it would be worth a good deal of trouble; but, in my opinion, if the patient has one useful eye, whether aphakic or normal, he should not be subjected to the hazard, apprehension, nerve strain, and cost of an operation, then the fitting of a contact lens, the expense of spectacles, and, after that, a course of training, all in order that, at best, a counterfeit sort of single binocular vision may be obtained.

DISCUSSION

Dr. M. Luther Kauffman: I had hoped that Dr. Cowan would present a method of obtaining satisfactory binocular function for patients with monocular aphakia. This is a great deal to expect, however, since the fundamental principles of optics remain the same as in the past.

It is the responsibility of the ophthalmologist to do all he can to prevent this condition of monocular aphakia when the other eye has satisfactory visual function, and to explain to the patient what the difficulties are when there is no choice in the matter. The too early removal of certain cataracts from one eye while the other eye retains good vision often causes the patient more difficulty than benefit.

Dr. Paul A. Rockwell: The use of contact lenses in cases of monocular aphakia has not been well discussed in the literature. In most of the published large series the authors have relied upon postcard inquiries, and careful objective evaluation has been lacking. For this reason, we at the Graduate Hospital are engaged in a program to study this problem as thoroughly as possible. We have about 50 patients who are being examined by screen, the Maddox rod, the synoptophore, and the stereoscope. This work is still in progress, so I shall not give any figures; however, at this stage we can confidently say that the use of a contact lens in patients with uniocular aphakia is a practicable and valuable procedure.

The majority of the patients have simultaneous macular perception, and some have a fair degree of stereoscopic vision. Whether this is foveal or peripheral we are not prepared to say. We have had very few patients who were unable or unwilling to wear a contact lens, and we attribute this experience to our using the "lacrilens." We think this lens is far superior to any of its predecessors.

Dr. Alfred Cowan: I believe that if a patient has one eye with useful vision both he and the ophthalmologist should be satisfied. If the ophthalmologist sees fit to employ it, and the patient can wear it, a contact lens is a very good means of correcting aphakia; but it will not enable a person with monocular aphakia to obtain good, comfortable binocular single vision.

Dr. Rockwell said that in his study of a series of aphakic patients the accommodation was not given serious consideration since the subjects were all over 40 years of age. I think a difference in accommodation of 2.50 D. is a serious consideration. No person could possibly be comfortable with this much difference between the two eyes.

# News and Comment

## ANNUAL MEETING OF AMERICAN MEDICAL ASSOCIATION

**New York, June 1-5, 1953**

*The following portion of the program of the 1953 American Medical Association Scientific Session relating to ophthalmology will be of interest to readers of this journal.*

### Combined Meeting of Section on Ophthalmology with Association for Research in Ophthalmology

Astor Gallery, Waldorf-Astoria

SECTION ON OPHTHALMOLOGY

### Tuesday, June 2—9 a. m.

**Chairman's Address** — FRANCIS H. ADLER, Philadelphia

**The Scleral Resection Operation for Retinal Detachment: An Evaluation of the Results**

PETER C. KRONFELD, Chicago, and DOHRMANN K. PISCHEL, San Francisco

**A Comparison of Scleral Resection and Scleral Folding in the Experimental Shortening of the Eye**

ANGELOS N. DELLAPORTA, Buffalo

**The Use of $P^{32}$ Diagnostically in Ocular Pathology**

ISADORE J. EISENBERG, IRVING H. LEOPOLD, and DAVID M. SKLAROFF, Philadelphia

**Ocular Dysmetria, Flutter-Like Oscillations of the Eyes, and Opsoclonus**

DAVID G. COGAN, Boston

**Xerophthalmia** — DANIEL G. VAUGHAN JR., San Jose, Calif.

**Dacryocystography: The Normal Lacrimal Tract**

BYRON H. DEMOREST and BENJAMIN MILDER, St. Louis

### Wednesday, June 3—9 a. m.

EXECUTIVE SESSION
ELECTION OF OFFICERS

**Address of Invited Foreign Guest** — A. FRANCESCHETTI, Geneva, Switzerland

**Uveitis in Children**

PHILLIPS THYGESON, San Jose, Calif., and MICHAEL J. HOGAN and SAMUEL J. KIMURA, San Francisco

**Uveitis: A Military Problem** — JOHN R. FAIR, Meridian, Ga.

**A Clinical Report of the Use of Three New Cycloplegic Drugs**

BERNARD C. GETTES, Philadelphia

**Very Early Vascular Signs in the Retina in Relation to Elevated Diastolic Blood Pressure**

HENRY MINSKY, New York

**Demonstration of New Instruments**

### Thursday, June 4—9 a. m.

**Doracaine for Rapid Anesthesia of the Cornea**
HENRY E. SCHLEGEL JR. and KENNETH C. SWAN, Portland, Ore.

**A Preliminary Report on the Ridley Operation**
WARREN S. REESE and TURGUT N. HAMDI, Philadelphia

**Contact Lenses in Aphakia** ELIZABETH F. CONSTANTINE and JOHN M. MCLEAN, New York

**Isonicotinic Acid Hydrazide in Ophthalmology**
THEODORE F. SCHLAEGEL JR. and LOUIS N. HUNGERFORD, Indianapolis

**Fibrin Film in the Treatment of Corneal Diseases** C. WILLIAM WEISSER, Pittsburgh

**Experiences with a Magnetic Implant for Cosmetic Improvement of the Enucleation Procedure over a Five-Year Period** RICHARD C. TROUTMAN, New York

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY

### Monday, June 1—1 p. m.

Einhorn Auditorium, Lenox Hill Hospital

**Clinical Aspects of Vitreous Body Pathology** CHARLES L. SCHEPENS

**Physicochemical Studies on the Vitreous Body** L. VARGA and ENDRE A. BALAZS

**Properties of the Fibrous Component of the Vitreous Body** A. GEDEON MATOLTSY

**Application of Paper Electrophoresis to the Study of the Soluble Vitreous Humor Proteins** LEROY SCHIELER

**Ultraviolet Absorption of the Vitreous Body** ENDRE A. BALAZS

**Studies on the Cornea: I. The Fine Structure of the Rat Cornea** MARIE A. JAKUS

GENERAL DISCUSSION ON VITREOUS
CHARLES L. SCHEPENS, Moderator

### Tuesday, June 2—2 p. m.

**The Recording of the Electroretinogram in Humans and in Animals**
I. H. WAGMAN, JOSEPH WALDMAN, DAVID NAIDOFF, L. B. FEINSCHIL, and R. CHAHAN

**Electroretinography in Cases of Night Blindness** LORRIN A. RIGGS

**The Origin of the Electroretinogram** W. K. NOELL

**Detection of Intraocular Tumors Using Radioactive Phosphorus**
CHARLES I. THOMAS, JACK S. KROHMER, and JOHN P. STORAASLI

**Investigation of Corticoid Materials in Intraocular Fluids of Normal and Diseased Experimental Animal and Human Eyes**
HARRY GREEN, VIRGINIA L. WEIMER, and IRVING H. LEOPOLD

**Studies on the Nature of the Exophthalmos-Producing Principle of Hypophysial Extracts** GEORGE K. SMELSER and V. OZANICS

### Wednesday, June 3—2 p. m.

**The Influence of ACTH on the Reactivity of the Capillary Bed in the Eye**
L. VON SALLMANN, B. PILLAT, and M. M. POWERS

**A New Method for Measuring Binocular Fusion Compulsion** GERHARD A. BRECHER

**The Effect of Oxygen, Glucose, and Glutamic Acid on the Reversible Cation Shift of the Lens**

JOHN E. HARRIS, JAMES D. HAUSCHILDT, and LORETTA T. NORDQUIST

**Effects of Intracarotid Injection of a Basic Dye on the Ciliary Body**

ELMER J. BALLINTINE and LAWRENCE PETERS

**The Composition of the Polysaccharide of the Bovine Lens Capsule and Its Topical Distribution** Z. DISCHE and E. BORENFREUND

### Thursday, June 4—2 p. m.

**The Nutritional Supply of Corneal Regions in Experimental Animals: III. Further Studies on the Corneal Transport of Inorganic Ions**

ALFRED M. POTTS, DORIS GOODMAN, and LORAND V. JOHNSON

**The Role of Metabolism in the Hydration of Isolated Bovine Lens and Cornea**

BERNARD SCHWARTZ, BETTY DANES, and P. J. LEINFELDER

**Experimental Granulomatous Uveitis: Studies on the Mechanism of the Contralateral Reaction After the Use of Horse Serum in Rabbits**

T. F. SCHLAEGEL, FRED M. WILSON, and JACK TADMAN

**Treatment of Experimental Ocular Tuberculosis with Isoniazid**

PHILIP KNAPP and LUDWIG VON SALLMANN

**Healing of the Posterior Lens Capsule and Lens-Induced Endophthalmitis: An Experimental Study** WOOD LYDA, RICHEY L. WAUGH JR., and GEORGE H. HAIK

**Extramedullary Hematopoiesis in and Around the Eye**

ALGERNON B. REESE and FREDERICK C. BLODI

### Section on Dermatology and Syphilology

Baroque Room, Belmont Plaza

### Wednesday, June 3, p. m.

**The Diagnosis and Treatment of Carcinoma of the Eyelids**

EUGENE F. TRAUB, New York

*Fifth of six papers to be read at afternoon session, after election of officers.*

### Section on Military Medicine

North Ballroom, Astor Hotel

### Wednesday, June 3, p. m.

**Observations of the Fundus Oculi During Blackout**

T. D. DUANE and EDWARD L. BECKMAN, Johnsville, Pa. Discussion to be opened by VICTOR BYRNES, Randolph Field, Texas.

*Last of six papers to be read at afternoon session, after election of officers.*

## SOCIETY NEWS

**Société française d'ophtalmologie.**—The 59th meeting of this society was held in Paris, June 22 through 26, 1952. It was, as usual, a very international gathering. Most of the non-French delegates came from European countries, but the Western Hemisphere was represented by Dr. W. Collinson, of Boston; Dr. Pacheco-Luna, of Guatemala city, and Dr. de Amarall, of Brazil.

For the last 30 years the Société française d'ophtalmologie has been accustomed to distribute to its members, sometime before the annual meeting, a monograph, written especially for that occasion, to be discussed at one of the sittings of the society. These volumes still come under the name of *"rapports,"* although they have gradually become so large that they have little in common with what is usually known as *rapports* or symposium reports.

This year the monograph was by Dr. André Dubois-Poulsen, on the visual field (Le champ visuel: Topographie normale et pathologique de ses sensibilités). The author had been working on it for over seven years, and it is at present the most comprehensive book on the visual fields. It is somewhat more comprehensive than previous publications (Traquair, Malbrán, Lauber) in that it considers in greater detail the normal, physiological visual field, and therefore, to a great extent, the physiology of the normal retina. The book has over 1,200 pages with 820 illustrations. It was distributed free to all members of the Society but can be purchased by others for 6,500 francs (about $18.50) by applying to the publisher, Masson & Cie, 120 Boulevard Saint-Germain, Paris.

The discussion of this monograph was scheduled for Tuesday, June 24, and on the same day other papers were read on the same subject. G. Jayle and associates (Marseilles) reported on the correlation between clinical findings and visual fields taken with Goldmann's perimeter in 2,000 patients. L. Guillaumat and A. Robin (Paris) had a large series of fields taken in cases of intracranial, but nontraumatic, diseases. The findings usually conformed to established knowledge, but in some instances they were unexpected and the fields could be explained only by pressure on blood vessels. J. Kluyskens and J. Titeca (Gent and Brussels) reported on the electroencephalographic findings in visual-field studies. Normal subjects and patients having an organic disturbance showed good correlation, whereas important discrepancies were found when the disturbance was only functional. This observation could be used in the detection of malingering. R. Hermans (Brussels) made a study of fluorescent lighting. Its flickering is the cause of cerebral activity, and this explains visual symptoms and fatigue. A. Franceschetti and associates (Geneva) reported on a case of primary glaucoma in which careful field studies suggested a homonymous depression; this led to the discovery of a pituitary tumor, which showed greater extension on one side.

June 22: The first day was devoted to papers on neuro-ophthalmology.

A. Hoorens (Gent) stressed the importance of the cervical sympathetic nerve fibers in pupillary movements and produced miosis and mydrasis. Druault-Toufesco (Tours) claimed that ophthalmologists are prone to study only the pupillary reflexes, whereas investigation of static anomalies can be just as valuable. G. Bonamour (Lyons) reported a case of Adie syndrome following chickenpox. P. Marx (Rouen) reported the case of a child who had paralysis both of the pupillary sphincter and of the accommodation in one eye only, due to diphtheria. P. Brégeat and associates (Paris) reported a case of cirsoid aneurysm of the retina and of the brain. They stressed the different methods of examination: color retinography, orbital roentgenography and tomography, carotid arteriography, orbital phlebography, and phlebography of veins located within the bones. Calmettes and associates (Toulouse) reported on a case of pulsating exophthalmos. The patient had cranial metastasis of a thyroid tumor with bone destruction. The carotid artery was dilated as shown in arteriograms, and was the cause of the pulsating exophthalmos. L. Paufique and R. Etienne (Lyons), during the course of tuberculous meningitis, treated with streptomycin, observed three cases in which field studies suggested chiasmal involvement. Surgical exploration revealed a tuberculoma of the chiasm and permitted local streptomycin therapy. P. Desvignes and M. Brun (Paris) considered the changes in belief concerning the etiology of so-called infectious optic neuritis. M. Marin-Amat (Madrid) read a paper on the trigeminal nerve in its relation to visual organs. A. Larmande and R. Susini (Algiers) reported on two brothers with Laurence-Moon-Biedl disease. The electroencephalogram showed that subcortical areas were affected, particularly the

diencephalon. H. X. Man and J. Gruner (Paris) reported on the pathology in a case of cortical blindness, i. e., softening of the gyrus angularis on one side and of the area of the posterior central artery on the other.

June 23: The papers read were on diseases of the uvea and on glaucoma. H. Chavanne and P. G. Moreau (Lyons) showed sections in a case of acute melanoma of the iris. N. Trantas (Athens) reported a case of cyst of the iris which grew slowly until it reached a certain size, when it emptied. The process then started again. P. and J. Lavat (Paris) observed several cases of toxoplasmosis. They stressed the point that serological tests are not entirely reliable as a means of diagnosis. B. Sezer (Istanbul) claimed to have isolated a virus specific for Behcet's disease. It produces encephalitis in the mouse, an experimental disease in the rabbit, and typical alterations in the chorioallantois of the egg. Complement fixation and neutralization tests with the patient's serum are constantly positive. G. P. Sourdille (Nantes) reviewed the results of iridencleisis in 400 patients. Tension was definitely better when filtration was present. R. Weekers (Liége) had measured the outflow of the aqueous with an electronic tonometer and the use of Friedenwald's charts. He concluded that retrociliary diathermy was effective in that it reduced the formation of aqueous and that iridencleisis acted by lowering the resistance to outflow of the aqueous. A. G. Ourgaud and associates (Marseilles) stressed the importance of the psychological background in the etiology of glaucoma. J. Francois (Gent) had experimented with electroretinography in cases of glaucoma. In congestive glaucoma, the electroetinogram tends to be supernormal. In primary glaucoma it is normal except in cases in which retinal degeneration is far advanced; it is then subnormal. In absolute glaucoma it is either subnormal or negative. In secondary glaucoma the b-wave depends on the amount of retinal degeneration. Operation does not seem to alter the electroretinogram. M. and I. Stankovic (Belgrade) stressed the value of photophobia as an isolated symptom in the early stages of congenital glaucoma.

June 25: The papers read were on the retina and its diseases.

P. Guillot (Marseilles) found that in determining the cause of the syndrome of obstruction of the central retinal artery it is useful to lay the patient down with the head lower than the body. If there is only atony of the artery, the blood flow will be resumed. If there is an organic block due, for instance, to embolism or thrombosis, the blood flow will not improve. M. Ardouin and associates (Rennes) observed that measure of the retinal blood pressure by Bailliart's method is valuable in cases of the hyperpiesis of pregnancy. A change in the normal 1:2 relation of the retinal to the humoral diastolic pressure is the earliest sign of toxemia. After delivery, the determination has a prognostic value and will enable one to foresee whether the patient will recover entirely or whether hypertensive disease will develop. S. Schiff-Wertheimer reported cases of retinal detachment in which the immediate results of operation were poor and in which in the course of time the retina gradually reattached. R. Onfray and associates (Paris) attempted to correlate fundus changes and biopsy findings in the kidney and adrenal gland in patients with high blood pressure and retinitis. L. Alaerts (Brussels) reported on 10 cases of flat intraretinal cyst. V. Bischler (Geneva) reported the history of a child with a yellow patch similar to that in the cases of vitelliform cysts published by Zanen and Rausin. The cause was unknown. J. Zanen and associates (Brussels) showed photographs of unusual retinal anomalies of debatable diagnosis. E. Joseph and G. Offret (Paris) gave the very interesting histories of two cases of bilateral retinoblastoma. One eye had been enucleated, and the glioma in the second eye had been destroyed by electrocoagulation. The cure seemed permanent, one child having been observed for seven years and the other for three years after the electrocoagulation. J. Beauvieux and Pesme (Bordeaux) discussed the pseudoglioma group and the congenital anomalies of the retina. A. Bronner and A. Lobstein (Strasbourg) stressed the diagnostic value of the retinal blood pressure in obstructions of the carotid, ophthalmic, and retinal arteries. Deviations from normal varied according to the level of the lesion and the presence

or absence of superimposed spasm. E. B. Streiff (Lausanne) suggested that keratoconus and retinitis pigmentosa may be genetically linked. He reported three cases of such occurrence. J. Mawas (Paris) projected photographs showing vasomotor nerves in the retina. J. Gallois (Paris) had found glutamic acid useful in various retinal diseases.

June 20: The last day was devoted to so-called free papers, on subjects not on the agenda for the 1952 meeting.

A. Couadau and Campan (Toulouse) gave a favorable report on general anesthesia in ophthalmic operations, and especially on the use of curare in local anesthesia. J. Babel and J. B. Bourquin (Geneva) had grafted small fragments of the cornea of one rabbit between the layers of the cornea of another. In some animals the transplant remained transparent. R. Hugonier (Lyons) gave a very favorable report of his experience with the Lancaster red-green test in diplopia. A. Fritz (Brussels) reported on a personal method for treating false projection in squint. G. Sevrin (Charleroi) reported the history of two patients with supranuclear and monocular paralysis of the superior rectus and inferior oblique. The diagnosis was discussed. Both patients had been eventually operated on by J. Malbrán (Buenos Aires), with favorable results. C. Thomas and associates (Nancy) observed patients with venereal lymphogranuloma (Nicolas-Favre disease) with conjunctival signs similar to those in tularemia. In their patients the pathology of the conjunctiva and that of the corresponding lymph node were very similar. P. Jeandelize and associates (Nancy) expressed the opinion that in the early stages of cataract ascorbic acid was useful, especially with associated endocrine therapy. G. Calamandrei and L. Mazzanti (Florence) investigated the action of cortisone on the nervous system. They were unable to reach any definite conclusion. H. Arruga (Barcelona) showed a film of several Ridley operations for cataract. He had performed 13 such operations. Twice the plastic lens fell into the vitreous. The reaction of the iris was usually marked for some time after the operation. Jose Barraquer, during the discussion, said that he was able to avoid this reaction by injecting cortisone into the anterior chamber at the end of the operation. F. Orzalesi and M. Miglior (Cagliari) claimed that they had inactivated the virus of herpes, in vitro, with lysozyme. E. Hervouet (Nantes) showed slides illustrating a rare anomaly. The eye had been enucleated for suspected glioma. Pathologic examination revealed a persistent Cloquet canal almost completely covered with normal retinal tissue.

*Other Events.*—Several surgical films were shown on the afternoon of Tuesday, June 24, and operative sessions were organized, as usual, in most Paris ophthalmic hospitals on two other afternoons. On Monday, June 23, Arnold Sorsby, of London, gave an interesting lecture in Lariboisière Hospital on hereditary diseases of the fundus. He was able to show pictures of the fundus in the early stages of disease which are not usually recognized.

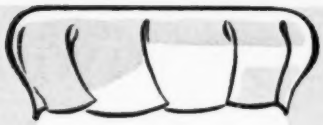
During the congress there were the usual social activities: an excursion to the two Trianon palaces of Versailles on Wednesday afternoon, and the traditional banquet on Tuesday evening, with Dr. Bailliart presiding.

The present reviewer having finished his four-year term as secretary-general, Dr. Marcel Kalt was elected to replace him. Henceforward all correspondence should be addressed to Dr. Marcel Kalt, Secretaire général de la Société française d'ophtalmologie 81, rue Saint Lazare, Paris (9°) France.

The 1953 meeting of the society will be held in Paris, June 21 through 25.

EDWARD HARTMANN, M.D.

**Section on Ophthalmology of the College of Physicians of Philadelphia.**—At the meeting of the Section on Nov. 19, 1953, at the College of Physicians Building, the Sixteenth Annual deSchweinitz Lecture will be presented by Dr. Alan C. Woods, Baltimore, on the subject "Pathogenesis and Treatment of Ocular Tuberculosis."



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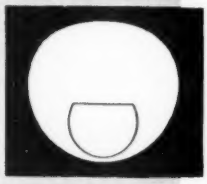

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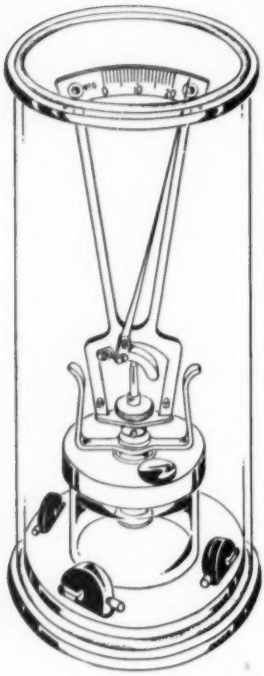

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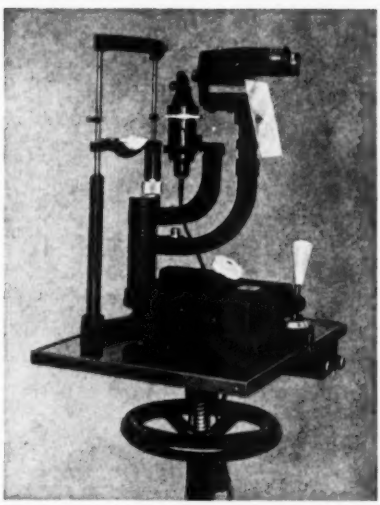

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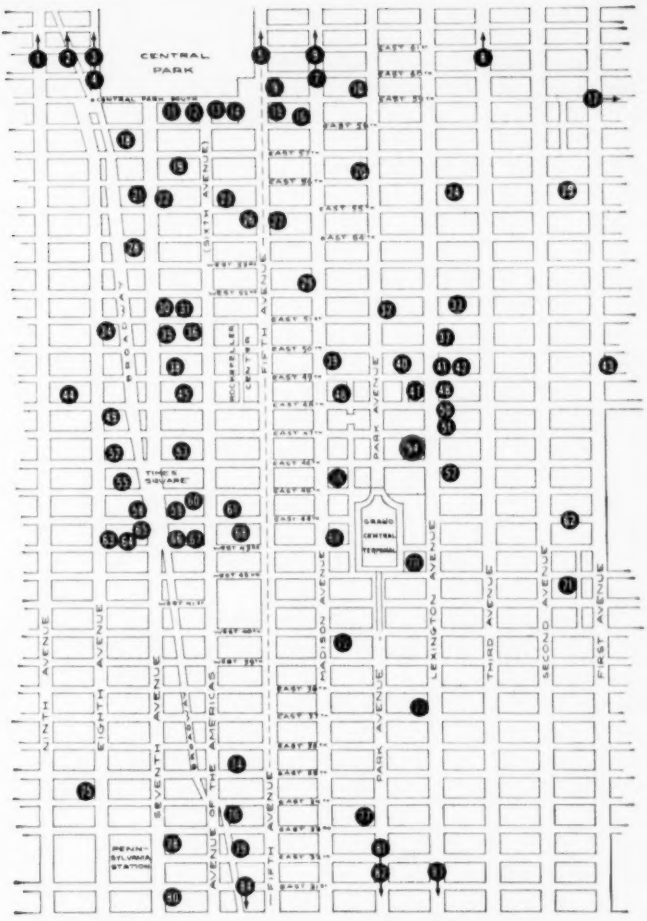


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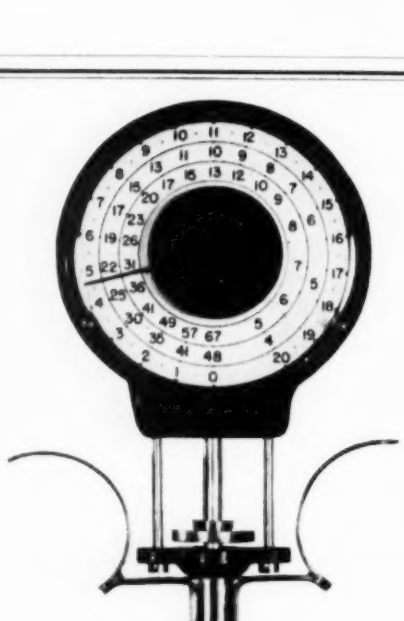

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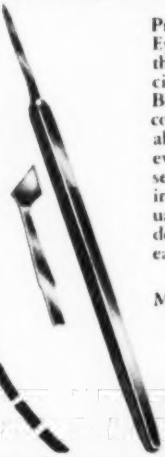

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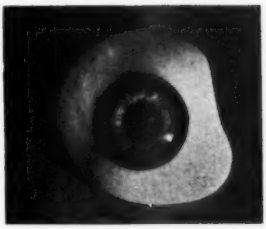

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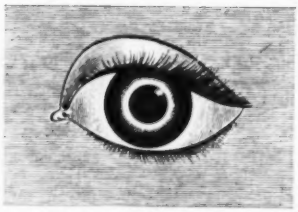

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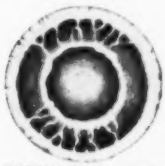

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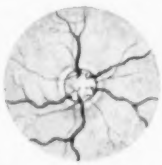

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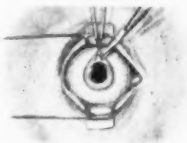

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